

DESCRIPTIONENZYMATIC NUCLEIC ACID TREATMENT OF DISEASES OR CONDITIONS
RELATED TO HEPATITIS C VIRUS INFECTION

This patent application is a continuation-in-part of Blatt *et al.*, USSN (not yet
 5 assigned), filed July 7, 2000, which is a continuation-in-part of Blatt *et al.*, 09/504,321, filed
 February 15, 2000, which is a continuation-in-part of Blatt *et al.*, USSN 09/274,553, filed
 March 23, 1999, which is a continuation-in-part of Blatt *et al.*, USSN 09/257,608, filed
 February 24, 1999 (abandoned), which claims priority from Blatt *et al.*, USSN 60/100,842,
 10 filed September 18, 1998, and McSwiggen *et al.*, USSN 60/083,217 filed April 27, 1998, all
 of these earlier applications are entitled "ENZYMATIC NUCLEIC ACID TREATMENT OF
 DISEASES OR CONDITIONS RELATED TO HEPATITIS C VIRUS INFECTION". Each
 of these applications are hereby incorporated by reference herein in their entirety including
 the drawings.

Technical Field Of The Invention

15 This invention relates to methods and reagents for the treatment of diseases or
 conditions relating to the hepatitis C virus infection.

Background Of The Invention

The following is a discussion of relevant art, none of which is admitted to be prior art
 to the present invention.

20 In 1989, the Hepatitis C Virus (HCV) was determined to be an RNA virus and was
 identified as the causative agent of most non-A non-B viral Hepatitis (Choo *et al.*, *Science*.
 1989; 244:359-362). Unlike retroviruses such as HIV, HCV does not go through a DNA
 replication phase and no integrated forms of the viral genome into the host chromosome have
 been detected (Houghton *et al.*, *Hepatology* 1991;14:381-388). Rather, replication of the coding
 25 (plus) strand is mediated by the production of a replicative (minus) strand leading to the
 generation of several copies of plus strand HCV RNA. The genome consists of a single,
 large, open-reading frame that is translated into a polyprotein (Kato *et al.*, *FEBS Letters*. 1991;

280: 325-328). This polyprotein subsequently undergoes post-translational cleavage, producing several viral proteins (Leinbach *et al.*, *Virology*. 1994: 204:163-169).

Examination of the 9.5-kilobase genome of HCV has demonstrated that the viral nucleic acid can mutate at a high rate (Smith *et al.*, *Mol. Evol.* 1997 45:238-246). This rate of mutation has led to the evolution of several distinct genotypes of HCV that share approximately 70% sequence identity (Simmonds *et al.*, *J. Gen. Virol.* 1994;75 :1053-1061). It is important to note that these sequences are evolutionarily quite distant. For example, the genetic identity between humans and primates such as the chimpanzee is approximately 98%. In addition, it has been demonstrated that an HCV infection in an individual patient is composed of several distinct and evolving quasispecies that have 98% identity at the RNA level. Thus, the HCV genome is hypervariable and continuously changing. Although the HCV genome is hypervariable, there are 3 regions of the genome that are highly conserved. These conserved sequences occur in the 5' and 3' non-coding regions as well as the 5'-end of the core protein coding region and are thought to be vital for HCV RNA replication as well as translation of the HCV polyprotein. Thus, therapeutic agents that target these conserved HCV genomic regions may have a significant impact over a wide range of HCV genotypes. Moreover, it is unlikely that drug resistance will occur with enzymatic nucleic acids specific to conserved regions of the HCV genome. In contrast, therapeutic modalities that target inhibition of enzymes such as the viral proteases or helicase are likely to result in the selection for drug resistant strains since the RNA for these viral encoded enzymes is located in the hypervariable portion of the HCV genome.

After initial exposure to HCV, the patient will experience a transient rise in liver enzymes, which indicates that inflammatory processes are occurring (Alter *et al.*, *IN*: Seeff LB, Lewis JH, eds. *Current Perspectives in Hepatology*. New York: Plenum Medical Book Co; 1989:83-89). This elevation in liver enzymes will occur at least 4 weeks after the initial exposure and may last for up to two months (Farci *et al.*, *New England Journal of Medicine*. 1991:325:98-104). Prior to the rise in liver enzymes, it is possible to detect HCV RNA in the patient's serum using RT-PCR analysis (Takahashi *et al.*, *American Journal of Gastroenterology*. 1993;88:2:240-243). This stage of the disease is called the acute stage and usually goes undetected since 75% of patients with acute viral hepatitis from HCV infection are asymptomatic. The remaining 25% of these patients develop jaundice or other symptoms of hepatitis.

Acute HCV infection is a benign disease, however, and as many as 80% of acute HCV patients progress to chronic liver disease as evidenced by persistent elevation of serum alanine aminotransferase (ALT) levels and by continual presence of circulating HCV RNA (Sherlock, *Lancet* 1992; 339:802). The natural progression of chronic HCV infection over a 10 to 20 year period leads to cirrhosis in 20 to 50% of patients (Davis *et al.*, *Infectious Agents and Disease* 1993;2:150:154) and progression of HCV infection to hepatocellular carcinoma has been well documented (Liang *et al.*, *Hepatology*. 1993; 18:1326-1333; Tong *et al.*, *Western Journal of Medicine*, 1994; Vol. 160, No. 2: 133-138). There have been no studies that have determined sub-populations that are most likely to progress to cirrhosis and/or hepatocellular carcinoma, thus all patients have equal risk of progression.

It is important to note that the survival for patients diagnosed with hepatocellular carcinoma is only 0.9 to 12.8 months from initial diagnosis (Takahashi *et al.*, *American Journal of Gastroenterology*. 1993;88:2:240-243). Treatment of hepatocellular carcinoma with chemotherapeutic agents has not proven effective and only 10% of patients will benefit from surgery due to extensive tumor invasion of the liver (Trinchet *et al.*, *Presse Medicine*. 1994:23:831-833). Given the aggressive nature of primary hepatocellular carcinoma, the only viable treatment alternative to surgery is liver transplantation (Pichlmayr *et al.*, *Hepatology*. 1994:20:33S-40S).

Upon progression to cirrhosis, patients with chronic HCV infection present with clinical features, which are common to clinical cirrhosis regardless of the initial cause (D'Amico *et al.*, *Digestive Diseases and Sciences*. 1986;31:5: 468-475). These clinical features may include: bleeding esophageal varices, ascites, jaundice, and encephalopathy (Zakim D, Boyer TD. *Hepatology a textbook of liver disease*. Second Edition Volume 1. 1990 W.B. Saunders Company. Philadelphia). In the early stages of cirrhosis, patients are classified as compensated meaning that although liver tissue damage has occurred, the patient's liver is still able to detoxify metabolites in the blood-stream. In addition, most patients with compensated liver disease are asymptomatic and the minority with symptoms report only minor symptoms such as dyspepsia and weakness. In the later stages of cirrhosis, patients are classified as decompensated meaning that their ability to detoxify metabolites in the bloodstream is diminished and it is at this stage that the clinical features described above will present.

In 1986, D'Amico *et al.* described the clinical manifestations and survival rates in 1155 patients with both alcoholic and viral associated cirrhosis (D'Amico *supra*). Of the 1155 patients, 435 (37%) had compensated disease although 70% were asymptomatic at the beginning of the study. The remaining 720 patients (63%) had decompensated liver disease with 78% presenting with a history of ascites, 31% with jaundice, 17% had bleeding and 16% had encephalopathy. Hepatocellular carcinoma was observed in six (.5%) patients with compensated disease and in 30 (2.6%) patients with decompensated disease.

Over the course of six years, the patients with compensated cirrhosis developed clinical features of decompensated disease at a rate of 10% per year. In most cases, ascites was the first presentation of decompensation. In addition, hepatocellular carcinoma developed in 59 patients who initially presented with compensated disease by the end of the six-year study.

With respect to survival, the D'Amico study indicated that the five-year survival rate for all patients on the study was only 40%. The six-year survival rate for the patients who initially had compensated cirrhosis was 54% while the six-year survival rate for patients who initially presented with decompensated disease was only 21%. There were no significant differences in the survival rates between the patients who had alcoholic cirrhosis and the patients with viral related cirrhosis. The major causes of death for the patients in the D'Amico study were liver failure in 49%; hepatocellular carcinoma in 22%; and, bleeding in 13% (D'Amico *supra*).

Chronic Hepatitis C is a slowly progressing inflammatory disease of the liver, mediated by a virus (HCV) that can lead to cirrhosis, liver failure and/or hepatocellular carcinoma over a period of 10 to 20 years. In the US, it is estimated that infection with HCV accounts for 50,000 new cases of acute hepatitis in the United States each year (NIH Consensus Development Conference Statement on Management of Hepatitis C March 1997). The prevalence of HCV in the United States is estimated at 1.8% and the CDC places the number of chronically infected Americans at approximately 4.5 million people. The CDC also estimates that up to 10,000 deaths per year are caused by chronic HCV infection. The prevalence of HCV in the United States is estimated at 1.8% and the CDC places the number

of chronically infected Americans at approximately 4.5 million people. The CDC also estimates that up to 10,000 deaths per year are caused by chronic HCV infection.

Numerous well controlled clinical trials using interferon (IFN-alpha) in the treatment of chronic HCV infection have demonstrated that treatment three times a week results in lowering of serum ALT values in approximately 50% (range 40% to 70%) of patients by the end of 6 months of therapy (Davis *et al.*, *New England Journal of Medicine* 1989; 321:1501-1506; Marcellin *et al.*, *Hepatology*. 1991; 13:393-397; Tong *et al.*, *Hepatology* 1997;26:747-754; Tong *et al.*, *Hepatology* 1997 26(6): 1640-1645). However, following cessation of interferon treatment, approximately 50% of the responding patients relapsed, resulting in a "durable" response rate as assessed by normalization of serum ALT concentrations of approximately 20 to 25%.

In recent years, direct measurement of the HCV RNA has become possible through use of either the branched-DNA or Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) analysis. In general, the RT-PCR methodology is more sensitive and leads to more accurate assessment of the clinical course (Tong *et al.*, *supra*). Studies that have examined six months of type 1 interferon therapy using changes in HCV RNA values as a clinical endpoint have demonstrated that up to 35% of patients will have a loss of HCV RNA by the end of therapy (Marcellin *et al.*, *supra*). However, as with the ALT endpoint, about 50% of the patients relapse six months following cessation of therapy resulting in a durable virologic response of only 12% (Marcellin *et al.*, *supra*). Studies that have examined 48 weeks of therapy have demonstrated that the sustained virological response is up to 25% (NIH consensus statement: 1997). Thus, standard of care for treatment of chronic HCV infection with type 1 interferon is now 48 weeks of therapy using changes in HCV RNA concentrations as the primary assessment of efficacy (Hoofnagle *et al.*, *New England Journal of Medicine* 1997; 336(5) 347-356).

Side effects resulting from treatment with type 1 interferons can be divided into four general categories, which include 1. Influenza-like symptoms; 2. Neuropsychiatric; 3. Laboratory abnormalities; and, 4. Miscellaneous (Dusheiko *et al.*, *Journal of Viral Hepatitis*. 1994;1:3-5). Examples of influenza-like symptoms include; fatigue, fever, myalgia, malaise; appetite loss; tachycardia; rigors; headache and arthralgias. The influenza-like symptoms are usually short-lived and tend to abate after the first four weeks of dosing (Dushieko *et al.*,

supra). Neuropsychiatric side effects include: irritability, apathy; mood changes; insomnia; cognitive changes and depression. The most important of these neuropsychiatric side effects is depression and patients who have a history of depression should not be given type 1 interferon. Laboratory abnormalities include; reduction in myeloid cells including granulocytes, platelets and to a lesser extent red blood cells. These changes in blood cell counts rarely lead to any significant clinical sequelae (Dushieko *et al.*, *supra*). In addition, increases in triglyceride concentrations and elevations in serum alanine and aspartate aminotransferase concentration have been observed. Finally, thyroid abnormalities have been reported. These thyroid abnormalities are usually reversible after cessation of interferon therapy and can be controlled with appropriate medication while on therapy. Miscellaneous side effects include nausea; diarrhea; abdominal and back pain; pruritus; alopecia; and rhinorrhea. In general, most side effects will abate after 4 to 8 weeks of therapy (Dushieko *et al.*, *supra*).

Welch *et al.*, *Gene Therapy* 1996 3(11): 994-1001 describe *in vitro* and *in vivo* studies with two vector expressed hairpin ribozymes targeted against hepatitis C virus.

Sakamoto *et al.*, *J. Clinical Investigation* 1996 98(12): 2720-2728 describe intracellular cleavage of hepatitis C virus RNA and inhibition of viral protein translation by certain vector expressed hammerhead ribozymes.

Lieber *et al.*, *J. Virology* 1996 70(12): 8782-8791 describe elimination of hepatitis C virus RNA in infected human hepatocytes by adenovirus-mediated expression of certain hammerhead ribozymes.

Ohkawa *et al.*, 1997, *J. Hepatology*, 27; 78-84, describe *in vitro* cleavage of HCV RNA and inhibition of viral protein translation using certain *in vitro* transcribed hammerhead ribozymes.

Barber *et al.*, International PCT Publication No. *WO 97/32018*, describe the use of an adenovirus vector to express certain anti-hepatitis C virus hairpin ribozymes.

Kay *et al.*, International PCT Publication No. *WO 96/18419*, describe certain recombinant adenovirus vectors to express anti-HCV hammerhead ribozymes.

Yamada *et al.*, Japanese Patent Application No. *JP 07231784* describe a specific poly-(L)-lysine conjugated hammerhead ribozyme targeted against HCV.

Draper, U.S. Patent Nos. 5,610,054 and 5,869,253, describes enzymatic nucleic acid molecules capable of inhibiting replication of HCV.

- 5 Macejak *et al.*, 2000, *Hepatology*, 31, 769-776, describe enzymatic nucleic acid molecules capable of inhibiting replication of HCV.

SUMMARY OF THE INVENTION

This invention relates to enzymatic nucleic acid molecules directed to cleave RNA species of hepatitis C virus (HCV) and/or encoded by the HCV. In particular, applicant describes the selection and function of enzymatic nucleic acid molecules capable of specifically cleaving HCV RNA. Such enzymatic nucleic acid molecules may be used to treat diseases associated with HCV infection.

Due to the high sequence variability of the HCV genome, selection of enzymatic nucleic acid molecules for broad therapeutic applications would likely involve the conserved regions of the HCV genome. Specifically, the present invention describes enzymatic nucleic acid molecules that would cleave in the conserved regions of the HCV genome. Examples of conserved regions of the HCV genome include but are not limited to the 5'-Non Coding Region (NCR), the 5'-end of the core protein coding region, and the 3'- NCR. HCV genomic RNA contains an internal ribosome entry site (IRES) in the 5'-NCR which mediates translation independently of a 5'-cap structure (Wang *et al.*, 1993, *J. Virol.*, 67, 3338-44). The full-length sequence of the HCV RNA genome is heterologous among clinically isolated subtypes, of which there are at least 15 (Simmonds, 1995, *Hepatology*, 21, 570-583), however, the 5'-NCR sequence of HCV is highly conserved across all known subtypes, most likely to preserve the shared IRES mechanism (Okamoto *et al.*, 1991, *J. General Virol.*, 72, 2697-2704) In general, enzymatic nucleic acid molecules that cleave sites located in the 5' end of the HCV genome would be expected to block translation while enzymatic nucleic acid molecules that cleave sites located in the 3' end of the genome would be expected to block RNA replication. Therefore, one enzymatic nucleic acid molecule can be designed to cleave all the different isolates of HCV. According to the Applicant, enzymatic nucleic acid molecules designed against conserved regions of various HCV isolates will enable efficient inhibition of HCV replication in diverse patient populations and may ensure the effectiveness of the enzymatic nucleic acid molecules against HCV quasi species which evolve due to mutations in the non-conserved regions of the HCV genome.

In another preferred embodiment, the invention features the use of an enzymatic nucleic acid molecule, preferably in the hammerhead, NCH (Inozyme), G-cleaver, amberzyme, zinzyme and/or DNAzyme motif, to inhibit the expression of HCV RNA.

In yet another preferred embodiment, the invention features the use of an enzymatic nucleic acid molecule, preferably in the hammerhead, Inozyme, G-cleaver, amberzyme, zinzyme and/or DNAzyme motif, to inhibit the expression of HCV minus strand RNA.

By "inhibit" it is meant that the activity of HCV or level of RNAs or equivalent RNAs encoding one or more protein subunits of HCV is reduced below that observed in the absence of the nucleic acid molecules of the invention. In one embodiment, inhibition with enzymatic nucleic acid molecule preferably is below that level observed in the presence of an enzymatically inactive or attenuated molecule that is able to bind to the same site on the target RNA, but is unable to cleave that RNA. In another embodiment, inhibition of HCV genes with the nucleic acid molecule of the instant invention is greater than in the presence of the nucleic acid molecule than in its absence.

By "enzymatic nucleic acid molecule" it is meant a nucleic acid molecule which has complementarity in a substrate binding region to a specified gene target, and also has an enzymatic activity which is active to specifically cleave target RNA. That is, the enzymatic nucleic acid molecule is able to intermolecularly cleave RNA and thereby inactivate a target RNA molecule. These complementary regions allow sufficient hybridization of the enzymatic nucleic acid molecule to the target RNA and thus permit cleavage. One hundred percent complementarity is preferred, but complementarity as low as 50-75% may also be useful in this invention. The nucleic acids may be modified at the base, sugar, and/or phosphate groups. The term enzymatic nucleic acid is used interchangeably with phrases such as enzymatic nucleic acids, catalytic RNA, enzymatic RNA, catalytic DNA, aptazyme or aptamer-binding enzymatic nucleic acid, regulatable enzymatic nucleic acid, allosteric catalytic nucleic acid, allosteric enzymatic nucleic acid, allosteric ribozyme, catalytic oligonucleotides, nucleozyme, DNAzyme, RNA enzyme, endoribonuclease, endonuclease, minizyme, leadzyme, oligozyme or DNA enzyme. All of these terminologies describe nucleic acid molecules with enzymatic activity. The specific enzymatic nucleic acid molecules described in the instant application are not meant to be limiting and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it have a specific substrate binding site which is complementary to one or more of the target nucleic acid regions, and that it have nucleotide sequences within or surrounding that substrate binding site which

impart a nucleic acid cleaving activity to the molecule (Cech *et al.*, U.S. Patent No. 4,987,071; Cech *et al.*, 1988, JAMA).

By "nucleic acid molecule" as used herein is meant a molecule having nucleotides. The nucleic acid can be single, double, or multiple stranded and may comprise modified or unmodified nucleotides or non-nucleotides or various mixtures and combinations thereof.

By "enzymatic portion" or "catalytic domain" is meant that portion/region of the enzymatic nucleic acid essential for cleavage of a nucleic acid substrate (for example see Figure 1).

By "substrate binding arm" or "substrate binding domain" is meant that portion/region of an enzymatic nucleic acid which is complementary to (*i.e.*, able to base-pair with) a portion of its substrate. Generally, such complementarity is 100%, but can be less if desired. For example, as few as 10 bases out of 14 may be base-paired. Such arms are shown generally in Figure 1 and 3. That is, these arms contain sequences within an enzymatic nucleic acid which are intended to bring enzymatic nucleic acid and target RNA together through complementary base-pairing interactions. The enzymatic nucleic acid of the invention may have binding arms that are contiguous or non-contiguous and may be of varying lengths. The length of the binding arm(s) are preferably greater than or equal to four nucleotides; specifically 12-100 nucleotides; more specifically 14-24 nucleotides long. If two binding arms are chosen, the design is such that the length of the binding arms are symmetrical (*i.e.*, each of the binding arms is of the same length; *e.g.*, five and five nucleotides, six and six nucleotides or seven and seven nucleotides long) or asymmetrical (*i.e.*, the binding arms are of different length; *e.g.*, six and three nucleotides; three and six nucleotides long; four and five nucleotides long; four and six nucleotides long; four and seven nucleotides long; and the like).

By "Inozyme" or "NCH" motif is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **Figure 1** and in Ludwig *et al.*, International PCT publication Nos. WO 98/58058 and WO 98/58057. Inozymes possess endonuclease activity to cleave RNA substrates having a cleavage triplet NCH/, where N is a nucleotide, C is cytidine and H is adenosine, uridine or cytidine, and / represents the cleavage site. H is used interchangeably with X. Inozymes can also possess endonuclease activity to cleave RNA substrates having a cleavage triplet NCN/, where N is a nucleotide, C is cytidine, and /

represents the cleavage site. “T” in **Figure 1** represents an Inosine nucleotide, preferably a ribo-Inosine or xylo-Inosine nucleotide.

By “G-cleaver” motif is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **Figure 2** and in Eckstein *et al.*, International PCT publication No. WO/9916871. G-cleavers possess endonuclease activity to cleave RNA substrates having a cleavage triplet NYN/, where N is a nucleotide, Y is uridine or cytidine and / represents the cleavage site. G-cleavers may be chemically modified as is generally shown in **Figure 2**. G-cleavers can be used, for example, to cleave RNA substrates after an AUG/ triplet, where A is adenosine, U is uridine, G is guanosine, and / represents the cleavage site.

By “zinzyme” motif is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **Figure 3** and in Beigelman *et al.*, International PCT publication No. WO/9955857. Zinzymes possess endonuclease activity to cleave RNA substrates having a cleavage triplet including but not limited to YG/Y, where Y is uridine or cytidine, and G is guanosine and / represents the cleavage site. Zinzymes may be chemically modified to increase nuclease stability through chemical modifications or substitutions as generally shown in **Figure 3**, including substituting 2'-O-methyl guanosine nucleotides for guanosine nucleotides. In addition, differing nucleotide and/or non-nucleotide linkers can be used to substitute the 5'-gaaa-2' loop shown in the figure. Zinzymes represent a non-limiting example of an enzymatic nucleic acid molecule that does not require a ribonucleotide (2'-OH) group within its own nucleic acid sequence for activity.

By “amberzyme” motif is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **Figure 4** and in Beigelman *et al.*, International PCT publication No. WO/9955857. Amberzymes possess endonuclease activity to cleave RNA substrates having a cleavage triplet NG/N, where N is a nucleotide, G is guanosine, and / represents the cleavage site. Amberzymes may be chemically modified to increase nuclease stability through substitutions as are generally shown in **Figure 4**. In addition, differing nucleoside and/or non-nucleoside linkers can be used to substitute the 5'-gaaa-3' loops shown in the figure. Amberzymes represent a non-limiting example of an enzymatic nucleic acid molecule that does not require a ribonucleotide (2'-OH) group within its own nucleic acid sequence for activity.

By 'DNAzyme' is meant, an enzymatic nucleic acid molecule that does not require the presence of a 2'-OH group for its activity. In particular embodiments the enzymatic nucleic acid molecule may have an attached linker(s) or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. DNAzymes can be synthesized chemically or expressed endogenously *in vivo*, by means of a single stranded DNA vector or equivalent thereof. An example of a DNAzyme is shown in **Figure 5** and is generally reviewed in Usman *et al.*, International PCT Publication No. WO 95/11304; Chartrand *et al.*, 1995, *NAR* 23, 4092; Breaker *et al.*, 1995, *Chem. Bio.* 2, 655; Santoro *et al.*, 1997, *PNAS* 94, 4262; Breaker, 1999, *Nature Biotechnology*, 17, 422-423; and Santoro *et al.*, 2000, *J. Am. Chem. Soc.*, 122, 2433-39. Additional DNAzyme motifs can be selected by using techniques similar to those described in these references, and hence, are within the scope of the present invention.

By "sufficient length" is meant an oligonucleotide of greater than or equal to 3 nucleotides.

By "stably interact" is meant, interaction of the oligonucleotides with target nucleic acid (*e.g.*, by forming hydrogen bonds with complementary nucleotides in the target under physiological conditions).

By "equivalent" RNA to HCV is meant to include those naturally occurring RNA molecules associated with HCV infection in various animals, including human, rodent, primate, rabbit and pig. The equivalent RNA sequence also includes in addition to the coding region, regions such as 5'-untranslated region, 3'-untranslated region, introns, intron-exon junction and the like.

By "homology" is meant the nucleotide sequence of two or more nucleic acid molecules is partially or completely identical.

In one of the preferred embodiments of the inventions described herein, the enzymatic nucleic acid molecule is formed in a hammerhead or hairpin motif, but may also be formed in the motif of a hepatitis delta virus, group I intron, group II intron or RNase P RNA (in association with an RNA guide sequence), DNAzymes, NCH cleaving motifs (inozymes), or G-cleavers. Examples of such hammerhead motifs (Figure 1a) are described in Dreyfus,

supra, Rossi *et al.*, 1992, *AIDS Research and Human Retroviruses* 8, 183; Examples of hairpin motifs are described in Hampel *et al.*, EP0360257, Hampel and Tritz, 1989 *Biochemistry* 28, 4929, Feldstein *et al.*, 1989, *Gene* 82, 53, Haseloff and Gerlach, 1989, *Gene*, 82, 43, Hampel *et al.*, 1990 *Nucleic Acids Res.* 18, 299; Chowrira & McSwiggen, US. Patent No. 5,631,359. The hepatitis delta virus motif is generally described in Perrotta and Been, 1992 *Biochemistry* 31, 16. The RNase P motif is generally described in Guerrier-Takada *et al.*, 1983 *Cell* 35, 849; Forster and Altman, 1990, *Science* 249, 783; Li and Altman, 1996, *Nucleic Acids Res.* 24, 835. Examples of group II introns are generally described in Griffin *et al.*, 1995, *Chem. Biol.* 2, 761; Michels and Pyle, 1995, *Biochemistry* 34, 2965; Pyle *et al.*, International PCT Publication No. WO 96/22689. The Group I intron is generally described in Cech *et al.*, U.S. Patent 4,987,071. DNAzymes (Figure 4) are generally described in Usman *et al.*, International PCT Publication No. WO 95/11304; Chartrand *et al.*, 1995, *NAR* 23, 4092; Breaker *et al.*, 1995, *Chem. Bio.* 2, 655; Santoro *et al.*, 1997, *PNAS* 94, 4262; Breaker, 1999, *Nature Biotechnology*, 17, 422-423; Santoro *et al.*, 2000, *J. Am. Chem. Soc.*, 122, 2433-39). NCH cleaving motifs (Figure 1b) are generally described in Ludwig & Sproat, International PCT Publication No. WO 98/58058; and G-cleavers (Figure 1c) are generally described in Kore *et al.*, 1998, *Nucleic Acids Research* 26, 4116-4120 and Eckstein *et al.*, International PCT Publication No. WO 99/16871. Additional motifs contemplated by the instant invention include the Allozyme or allosteric enzymatic nucleic acid molecule (Breaker *et al.*, WO 98/43993, Shih *et al.*, U.S. Patent 5,589,332, George *et al.*, U.S. Patent 5,741,679), Amberzyme (Figure 2, Class I motif in Beigelman *et al.*, International PCT publication No. WO 99/55857) and Zinzyme (Figure 3, Class II motif in Beigelman *et al.*, International PCT publication No. WO 99/55857), all these references are incorporated by reference herein in their totalities, including drawings and can also be used in the present invention. These specific motifs are not limiting in the invention. Those skilled in the art will recognize that all that is important is that the enzymatic molecule have a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule (Cech *et al.*, U.S. Patent No. 4,987,071).

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another RNA sequence by either traditional Watson-Crick or other non-traditional types. In

reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its target or complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., enzymatic nucleic acid cleavage. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner et al., 1987, CSH Symp. Quant. Biol. LII pp.123-133; Frier et al., 1986, Proc. Nat. Acad. Sci. USA 83:9373-9377; Turner et al., 1987, J. Am. Chem. Soc. 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule which can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, 10 out of 10 being 50%, 60%, 70%, 80%, 90%, and 100% complementary). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

In a preferred embodiment the invention provides a method for producing a class of enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNAs encoding HCV proteins such that specific treatment of a disease or condition can be provided with either one or several enzymatic nucleic acids. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the enzymatic nucleic acid molecules can be expressed from DNA/RNA vectors that are delivered to specific cells. DNazymes can be synthesized chemically or expressed endogenously *in vivo*, by means of a single stranded DNA vector or equivalent thereof.

By "highly conserved sequence region" is meant, a nucleotide sequence of one or more regions in a target gene does not vary significantly from one generation to the other or from one biological system to the other.

Such enzymatic nucleic acid molecules are useful for the prevention of the diseases and conditions discussed above, and any other diseases or conditions that are related to the levels of HCV activity in a cell or tissue.

By "related" is meant that the inhibition of HCV RNAs and thus reduction in the level of respective viral activity will relieve to some extent the symptoms of the disease or condition.

In preferred embodiments, the enzymatic nucleic acid molecules have binding arms which are complementary to the target sequences in **Tables III-V**. Examples of such enzymatic nucleic acid molecules are also shown in **Tables III-VI**. Examples of such enzymatic nucleic acid molecules consist essentially of sequences defined in these tables.

Other sequences may be present which do not interfere with such cleavage.

By "consists essentially of" is meant that the active enzymatic nucleic acid molecule of the invention contains an enzymatic center or core equivalent to those in the examples, and binding arms able to bind RNA such that cleavage at the target site occurs. Other sequences may be present which do not interfere with such cleavage. Thus, a core region may, for example, include one or more loop or stem-loop structures, which do not prevent enzymatic activity. Such sequences can be designated as "X", for example, as in a loop or stem/loop structure. A core sequence for a hammerhead enzymatic nucleic acid can be CUGAUGAG X CGAA where X=GCCGUUAGGC or other stem II region known in the art. Similarly, for other enzymatic nucleic acid molecules of the instant invention, additional sequences may be present that do not interfere with the function of the nucleic acid molecule.

X may be a linker of ≥ 2 nucleotides in length, preferably 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 26, 30, where the nucleotides may preferably be internally base-paired to form a stem of preferably ≥ 2 base pairs. Alternatively or in addition, X may be a non-nucleotide linker. In yet another embodiment, the nucleotide linker (X) can be a nucleic acid aptamer, such as an ATP aptamer, HIV Rev aptamer (RRE), HIV Tat aptamer (TAR) and others (for a review see Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; and Szostak & Ellington, 1993, in *The RNA World*, ed. Gesteland and Atkins, pp. 511, CSH Laboratory Press). A "nucleic acid aptamer" as used herein is meant to indicate a nucleic acid sequence capable of interacting with a ligand. The ligand can be any natural or a synthetic molecule, including but not limited to a resin, metabolites, nucleosides, nucleotides, drugs, toxins, transition state analogs, peptides, lipids, proteins, amino acids, nucleic acid molecules, hormones, carbohydrates, receptors, cells, viruses, bacteria and others.

In yet another embodiment, the non-nucleotide linker (X) is as defined herein. The term "non-nucleotide" as used herein include either abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, or polyhydrocarbon compounds. Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, 18:6353 and *Nucleic Acids Res.* 1987, 15:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, 113:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, 113:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, 21:2585 and *Biochemistry* 1993, 32:1751; Durand *et al.*, *Nucleic Acids Res.* 1990,

18:6353; McCurdy et al., *Nucleosides & Nucleotides* 1991, 10:287; Jsche et al., *Tetrahedron Lett.* 1993, 34:301; Ono et al., *Biochemistry* 1991, 30:9914; Arnold et al., International Publication No. WO 89/02439; Usman et al., International Publication No. WO 95/06731; Dudycz et al., International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, 113:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine. Thus, in a preferred embodiment, the invention features an enzymatic nucleic acid molecule having one or more non-nucleotide moieties, and having enzymatic activity to cleave an RNA or DNA molecule.

Thus, in a first aspect, the invention features enzymatic nucleic acid molecules that inhibit gene expression and/or viral replication. These chemically or enzymatically synthesized nucleic acid molecules contain substrate binding domains that bind to accessible regions of their target mRNAs. The nucleic acid molecules also contain domains that catalyze the cleavage of RNA. The enzymatic nucleic acid molecules are preferably molecules of the hammerhead, Inozyme, DNAzyme, Zinzyme, Amberzyme, and/or G-cleaver motifs. Upon binding, the enzymatic nucleic acid molecules cleave the target mRNAs, preventing translation and protein accumulation. In the absence of the expression of the target gene, HCV gene expression and/or replication is inhibited.

In a preferred embodiment, enzymatic nucleic acid molecules are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection, infusion pump or stent, with or without their incorporation in biopolymers. In another preferred embodiment, the enzymatic nucleic acid molecule is administered to the site of HCV activity (e.g., hepatocytes) in an appropriate liposomal vehicle.

In another aspect of the invention, enzymatic nucleic acid molecules that cleave target molecules and inhibit HCV activity are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Enzymatic nucleic acid molecule expressing viral vectors could be constructed based on, but

not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant vectors capable of expressing the enzymatic nucleic acid molecules are delivered as described above, and persist in target cells. Alternatively, viral vectors may be used that provide for transient expression of enzymatic nucleic acid molecules. Such vectors might be repeatedly administered as necessary. Once expressed, the enzymatic nucleic acid molecules cleave the target mRNA. Delivery of enzymatic nucleic acid molecule expressing vectors could be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell (for a review see Couture and Stinchcomb, 1996, *TIG.*, 12, 510). In another aspect of the invention, enzymatic nucleic acid molecules that cleave target molecules and inhibit viral replication are expressed from transcription units inserted into DNA, RNA, or viral vectors. Preferably, the recombinant vectors capable of expressing the enzymatic nucleic acid molecules are locally delivered as described above, and transiently persist in smooth muscle cells. However, other mammalian cell vectors that direct the expression of RNA may be used for this purpose.

By "patient" is meant an organism which is a donor or recipient of explanted cells or the cells themselves. "Patient" also refers to an organism to which enzymatic nucleic acid molecules can be administered. Preferably, a patient is a mammal or mammalian cells. More preferably, a patient is a human or human cells.

As used in herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, e.g., specifically does not refer to a human. The cell may be present in a non-human multicellular organism, e.g., birds, plants and mammals such as cows, sheep, apes, monkeys, swine, dogs, and cats.

By RNA is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position (eg; 2'-OH) of a β -D-ribo-furanose moiety.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

These enzymatic nucleic acid molecules, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed above. For example, to treat a disease or condition associated with HCV levels, the patient may be treated, or other appropriate cells may be treated, as is evident to those skilled in the art.

5 In a further embodiment, the described molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic agents to treat liver failure, hepatocellular carcinoma, cirrhosis, and/or other disease states associated with HCV infection. Additional known therapeutic agents are those comprising antivirals,
10 interferon, and/or antisense compounds.

By "comprising" is meant including, but not limited to, whatever follows the word "comprising". Thus, use of the term "comprising" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of".
15 Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are
20 required or mandatory, but that other elements are optional and may or may not be present depending upon whether or not they affect the activity or action of the listed elements.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

25 The drawings will first briefly be described.

Drawings:

Figure 1 is a diagrammatic representation of a Hammerhead and an Inozyme motif. The examples shown are chemically stabilized with 2'-O-methyl substitutions (lower case), a 2'-deoxy-2'-C-allyl Uridine substitution at position U-4, and a 3'-terminal inverted deoxyabasic moiety. Conserved ribonucleotides are shown as rN, for example G-5, A-6, G-8, G-2, and I-15.1. Phosphorothioate internucleotide substitutions can be introduced, for example, at the four terminal 5' end nucleotides for increased stability to nuclease degradation. Stem II can be ≥ 2 base-pair long, preferably, 2, 3, 4, 5, 6, 7, 8, and 10 base-pairs long. Each N and N' is independently any base or non-nucleotide as used herein; X is adenosine, cytidine or uridine; Stems I-III are meant to indicate three stem-loop structures; stems I-III can be of any length and may be symmetrical or asymmetrical; arrow indicates the site of cleavage in the target RNA; Rz refers to enzymatic nucleic acid; Loop II may be present or absent. If Loop II is present it is greater than or equal to three nucleotides, preferably four nucleotides. The Loop II sequence is preferably 5'-GAAA-3' or 5'-GUUA-3'. Inozyme position 15.1 comprises an Inosine nucleotide, which can be ribo-Inosine or xylo-Inosine.

Figure 2 is a diagrammatic representation of a G-cleaver motif. The example shown is chemically stabilized with 2'-O-methyl substitutions, phosphorothioate internucleotide linkage substitutions, and a 3'-terminal inverted deoxyabasic moiety. In the figure, lower case a, g, c, and u represent 2'-O-methyl adenosine, guanosine, cytidine, and uridine nucleotides respectively; upper case A, G, C and U represent adenosine, guanosine, cytidine and uridine nucleotides respectively; "s" refers to phosphorothioate internucleotide linkages, and iB represents an 3'-terminal inverted deoxyabasic moiety.

Figure 3 is a diagrammatic representation of a zinzyme motif. The example shown is chemically stabilized with 2'-O-methyl substitutions, phosphorothioate internucleotide linkage substitutions, and a 3'-terminal inverted deoxyabasic moiety. C in the figure represents a 2'-deoxy-2'-amino cytidine nucleotide; lower case a, g, c, and u represent 2'-O-methyl adenosine, guanosine, cytidine, and uridine nucleotides respectively; uppercase A, G, C and U represent adenosine, guanosine, cytidine and uridine nucleotides respectively; "s" refers to phosphorothioate internucleotide linkages, and iB represents an 3'-terminal inverted deoxyabasic moiety. All of the ribo-guanosine nucleotides in the zinzyme motif can be replaced with 2'-O-methyl guanosine nucleotides. The 5'-gaaa-3' loop can be replaced with other nucleotide containing loop structures and/or non-nucleotide linkers, including PEG linkers. The guanosine nucleotide represented as G' in the figure can be replaced with either

2'-O-methyl guanosine, 5'-cytidine-adenosine-3', or 5'-cytidine-adenosine-adenosine-3' nucleotides and/or their corresponding 2'-O-methyl nucleotide derivatives.

Figure 4 is a diagrammatic representation of an amberzyme motif. The example shown is chemically stabilized with 2'-O-methyl substitutions and a 3'-terminal inverted deoxyabasic moiety. C in the figure represents a 2'-deoxy-2'-amino cytidine nucleotide; lower case a, g, c, and u represent 2'-O-methyl adenosine, guanosine, cytidine, and uridine nucleotides respectively; uppercase A, G, C and U represent adenosine, guanosine, cytidine and uridine nucleotides respectively; and iB represents an 3'-terminal inverted deoxyabasic moiety. The amberzyme motif can be further stabilized through introducing phosphorothioate internucleotide linkages, for example at the four terminal 5'-internucleotide linkages.

Figure 5 is a diagrammatic representation of a DNAzyme motif described generally, for example in Santoro *et al.*, 1997, *PNAS*, 94, 4262.

Figure 6 is a schematic representation of the Dual Reporter System utilized to demonstrate enzymatic nucleic acid mediated reduction of luciferase activity in cell culture.

Figure 7 shows a schematic view of the secondary structure of the HCV 5'UTR (Brown *et al.*, 1992, *Nucleic Acids Res.*, 20, 5041-45; Honda *et al.*, 1999, *J. Virol.*, 73, 1165-74). Major structural domains are indicated in bold. Enzymatic nucleic acid cleavage sites are indicated by arrows. Solid arrows denote sites amenable to amino-modified enzymatic nucleic acid inhibition. Lead cleavage sites (195 and 330) are indicated with oversized solid arrows.

Figure 8 shows a non-limiting example of a nuclease resistant enzymatic nucleic acid molecule. Binding arms are indicated as stem I and stem III. Nucleotide modifications are indicated as follows: 2'-O-methyl nucleotides, lowercase; ribonucleotides, uppercase G, A; 2'-amino-uridine, u; inverted 3'-3' deoxyabasic, **B**. The positions of phosphorothioate linkages at the 5'-end of each enzymatic nucleic acid are indicated by subscript "s". *H* indicates A, C or U ribonucleotide, *N'* indicates A, C G or U ribonucleotide in substrate, *n* indicates base complementary to the *N'*. The U4 and U7 positions in the catalytic core are indicated.

Figure 9 is a set of bar graphs showing enzymatic nucleic acid mediated inhibition of HCV-luciferase expression in OST7 cells. OST7 cells were transfected with complexes containing reporter plasmids (2 µg/mL), enzymatic nucleic acids (100 nM) and lipid. The

ratio of HCV-firefly luciferase luminescence/Renilla luciferase luminescence was determined for each enzymatic nucleic acid tested and was compared to treatment with the ICR, an irrelevant control enzymatic nucleic acid lacking specificity to the HCV 5'UTR (adjusted to 1). Results are reported as the mean of triplicate samples \pm SD. In **Figure 9A**, OST7 cells were treated with enzymatic nucleic acids (100 nM) targeting conserved sites (indicated by cleavage site) within the HCV 5'UTR. In **Figure 9B**, OST7 cells were treated with a subset of enzymatic nucleic acids to lead HCV sites (indicated by cleavage site) and corresponding attenuated core (AC) controls. Percent decrease in firefly/Renilla luciferase ratio after treatment with active enzymatic nucleic acids as compared to treatment with corresponding ACs is shown when the decrease is $\geq 50\%$ and statistically significant. Similar results were obtained with 50 nM enzymatic nucleic acid.

Figure 10 is a series of line graphs showing the dose-dependent inhibition of HCV/luciferase expression following enzymatic nucleic acid treatment. Active enzymatic nucleic acid was mixed with corresponding AC to maintain a 100 nM total oligonucleotide concentration and the same lipid charge ratio. The concentration of active enzymatic nucleic acid for each point is shown. **Figure 10A–E** shows enzymatic nucleic acids targeting sites 79, 81, 142, 195, or 330, respectively. Results are reported as the mean of triplicate samples \pm SD.

Figure 11 is a set of bar graphs showing reduction of HCV/luciferase RNA and inhibition of HCV-luciferase expression in OST7 cells. OST7 cells were transfected with complexes containing reporter plasmids (2 μ g /ml), enzymatic nucleic acids, BACs or SACs (50 nM) and lipid. Results are reported as the mean of triplicate samples \pm SD. In **Figure 11A** the ratio of HCV-firefly luciferase RNA/Renilla luciferase RNA is shown for each enzymatic nucleic acid or control tested. As compared to paired BAC controls (adjusted to 1), luciferase RNA levels were reduced by 40% and 25% for the site 195 or 330 enzymatic nucleic acids, respectively. In **Figure 11B** the ratio of HCV-firefly luciferase luminescence/Renilla luciferase luminescence is shown after treatment with site 195 or 330 enzymatic nucleic acids or paired controls. As compared to paired BAC controls (adjusted to 1), inhibition of protein expression was 70% and 40% for the site 195 or 330 enzymatic nucleic acids, respectively $P < 0.01$.

Figure 12 is a set a bar graphs showing interferon (IFN) alpha 2a and 2b dose response in combination with site 195 anti-HCV enzymatic nucleic acid treatment. **Figure 12A** shows data for IFN alfa 2a treatment. **Figure 12B** shows data for IFN alfa 2b treatment. Viral yield is reported from HeLa cells pretreated with IFN in units/ml (U/ml) as indicated for 4 h prior to infection and then treated with either 200 nM control (SAC) or site 195 anti-HCV enzymatic nucleic acid (195 RZ) for 24 h after infection. Cells were infected with a MOI = 0.1 for 30 min and collected at 24 h post infection. Error bars represent the S.D. of the mean of triplicate determinations.

Figure 13 is a line graph showing site 195 anti-HCV enzymatic nucleic acid dose response in combination with interferon (IFN) alpha 2a and 2b pretreatment. Viral yield is reported from HeLa cells pretreated for 4 h with or without IFN and treated with doses of site 195 anti-HCV enzymatic nucleic acid (195 RZ) as indicated for 24 h after infection. Anti-HCV enzymatic nucleic acid was mixed with control oligonucleotide (SAC) to maintain a constant 200 nM total dose of nucleic acid for delivery. Cells were infected with a MOI = 0.1 for 30 min and collected at 24 h post infection. Error bars represent the S.D. of the mean of triplicate determinations.

Figure 14 is a set of bar graphs showing data from consensus interferon (CIFN)/enzymatic nucleic acid combination treatment. **Figure 14 A** shows CIFN dose response with site 195 anti-HCV enzymatic nucleic acid treatment. Viral yield is reported from cells pretreated with CIFN in units/ml (U/ml) as indicated and treated with either 200 nM control (SAC) or site 195 anti-HCV enzymatic nucleic acid (195 RZ). **Figure 14B** shows site 195 anti-HCV enzymatic nucleic acid dose response with CIFN pretreatment. Viral yield is reported from cells pretreated with or without CIFN and treated with concentrations of site 195 anti-HCV enzymatic nucleic acid (195 RZ) as indicated. Anti-HCV enzymatic nucleic acid was mixed with control oligonucleotide (SAC) to maintain a constant 200 nM total dose of nucleic acid for delivery. Cells were infected with a MOI = 0.1 for 30 min. and collected at 24 h post infection. Error bars represent the S.D. of the mean of triplicate determinations.

Figure 15 is a bar graph showing enzymatic nucleic acid activity and enhanced antiviral effect of an anti-HCV enzymatic nucleic acid targeting site 195 used in combination with consensus interferon (CIFN). Viral yield is reported from cells treated as indicated.

BAC, cells were treated with 200 nM BAC (binding attenuated control) for 24 h after infection; CIFN+BAC, cells were treated with 12.5 U/ml CIFN for 4 h prior to infection and with 200 nM BAC for 24 h after infection; 195 RZ, cells were treated with 200 nM site 195 anti-HCV enzymatic nucleic acid for 24 h after infection; CIFN + 195 RZ, cells were treated with 12.5 U/ml CIFN for 4 h prior to infection and with 200 nM site 195 anti-HCV enzymatic nucleic acid for 24 h after infection. Cells were infected with a MOI = 0.1 for 30 min. Error bars represent the S.D. of the mean of triplicate determinations.

Figure 16 is a bar graph showing inhibition of a HCV-PV chimera replication by treatment with zinzyme enzymatic nucleic acid molecules targeting different sites within the HCV 5'-UTR compared to a scrambled attenuated core control (SAC) zinzyme.

Figure 17 is a bar graph showing inhibition of a HCV-PV chimera replication by antisense nucleic acid molecules targeting conserved regions of the HCV 5'-UTR compared to scrambled antisense controls.

Enzymatic Nucleic Acid Molecules

There are several known classes of enzymatic nucleic acid molecules capable of cleaving target RNA. In addition, several *in vitro* selection (evolution) strategies (Orgel, 1979, *Proc. R. Soc. London*, B 205, 435) have been used to evolve new nucleic acid catalysts capable of catalyzing cleavage and ligation of phosphodiester linkages (Joyce, 1989, *Gene*, 82, 83-87; Beaudry *et al.*, 1992, *Science* 257, 635-641; Joyce, 1992, *Scientific American* 267, 90-97; Breaker *et al.*, 1994, *TIBTECH* 12, 268; Bartel *et al.*, 1993, *Science* 261:1411-1418; Szostak, 1993, *TIBS* 17, 89-93; Kumar *et al.*, 1995, *FASEB J.*, 9, 1183; Breaker, 1996, *Curr. Op. Biotech.*, 7, 442; Santoro *et al.*, 1997, *Proc. Natl. Acad. Sci.*, 94, 4262; Tang *et al.*, 1997, *RNA* 3, 914; Nakamaye & Eckstein, 1994, *supra*; Long & Uhlenbeck, 1994, *supra*; Ishizaka *et al.*, 1995, *supra*; Vaish *et al.*, 1997, *Biochemistry* 36, 6495; all of these are incorporated by reference herein). Each can catalyze a series of reactions including the hydrolysis of phosphodiester bonds in *trans* (and thus can cleave other RNA molecules) under physiological conditions. **Table I** summarizes some of the characteristics of some of these enzymatic nucleic acids. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of an enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave

the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of an enzymatic nucleic acid molecule is advantageous over other technologies, since the concentration of enzymatic nucleic acid molecule necessary to affect a therapeutic treatment is lower. This advantage reflects the ability of the enzymatic nucleic acid molecule to act enzymatically. Thus, a single enzymatic nucleic acid molecule is able to cleave many molecules of target RNA. In addition, the enzymatic nucleic acid molecule is a highly specific inhibitor, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can be chosen to completely eliminate catalytic activity of an enzymatic nucleic acid molecule.

Nucleic acid molecules having an endonuclease enzymatic activity are able to repeatedly cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic nucleic acid molecules can be targeted to virtually any RNA transcript, and efficient cleavage achieved *in vitro* (Zaug *et al.*, 324, *Nature* 429 1986 ; Uhlenbeck, 1987 *Nature* 328, 596; Kim *et al.*, 84 *Proc. Natl. Acad. Sci. USA* 8788, 1987; Dreyfus, 1988, *Einstein Quart. J. Bio. Med.*, 6, 92; Haseloff and Gerlach, 334 *Nature* 585, 1988; Cech, 260 *JAMA* 3030, 1988; and Jefferies *et al.*, 17 *Nucleic Acids Research* 1371, 1989; Chartrand *et al.*, 1995, *Nucleic Acids Research* 23, 4092; Santoro *et al.*, 1997, *PNAS* 94, 4262).

Because of their sequence-specificity, *trans*-cleaving enzymatic nucleic acid molecules show promise as therapeutic agents for human disease (Usman & McSwiggen, 1995 *Ann. Rep. Med. Chem.* 30, 285-294; Christoffersen and Marr, 1995 *J. Med. Chem.* 38, 2023-2037). Enzymatic nucleic acid molecules can be designed to cleave specific RNA targets within the background of cellular RNA. Such a cleavage event renders the RNA non-

functional and abrogates protein expression from that RNA. In this manner, synthesis of a protein associated with a disease state can be selectively inhibited.

Enzymatic nucleic acid molecules that cleave the specified sites in HCV RNAs represent a novel therapeutic approach to infection by the hepatitis C virus. As shown herein, enzymatic nucleic acids are able to inhibit the activity of HCV and the catalytic activity of the enzymatic nucleic acids is required for their inhibitory effect. Those of ordinary skill in the art will find that it is clear from the examples described that other enzymatic nucleic acid molecules that cleave HCV RNAs may be readily designed and are within the invention.

Target sites

Targets for useful enzymatic nucleic acid molecules can be determined as disclosed in Draper *et al.*, WO 93/23569; Sullivan *et al.*, WO 93/23057; Thompson *et al.*, WO 94/02595; Draper *et al.*, WO 95/04818; McSwiggen *et al.*, US Patent No. 5,525,468 and hereby incorporated by reference herein in totality. Rather than repeat the guidance provided in those documents here, below are provided specific examples of such methods, not limiting to those in the art. Enzymatic nucleic acid molecules to such targets are designed as described in those applications and synthesized to be tested *in vitro* and *in vivo*, as also described. Such enzymatic nucleic acid molecules can also be optimized and delivered as described therein.

The sequence of HCV RNAs were screened for optimal enzymatic nucleic acid molecule target sites using a computer folding algorithm. Enzymatic nucleic acid cleavage sites were identified. These sites are shown in **Tables III-V** (All sequences are 5' to 3' in the tables). The nucleotide base position is noted in the tables as that site to be cleaved by the designated type of enzymatic nucleic acid molecule. The nucleotide base position is noted in the tables as that site to be cleaved by the designated type of enzymatic nucleic acid molecule.

Because HCV RNAs are highly homologous in certain regions, some enzymatic nucleic acid molecule target sites are also homologous. In this case, a single enzymatic nucleic acid molecule will target different classes of HCV RNA. The advantage of one enzymatic nucleic acid molecule that targets several classes of HCV RNA is clear, especially in cases where one or more of these RNAs may contribute to the disease state.

Enzymatic nucleic acid molecules were designed that could bind and were individually analyzed by computer folding (Jaeger *et al.*, 1989 *Proc. Natl. Acad. Sci. USA*, 86, 7706) to assess whether the enzymatic nucleic acid molecule sequences fold into the appropriate secondary structure. Those enzymatic nucleic acid molecules with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 bases on each arm are able to bind to, or otherwise interact with, the target RNA. Enzymatic nucleic acid molecules were designed to anneal to various sites in the mRNA message. The binding arms are complementary to the target site sequences described above.

Nucleic acid Synthesis

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, antisense oligonucleotides, hammerhead or the Inozyme enzymatic nucleic acids) are preferably used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

The method of synthesis used for normal RNA including certain enzymatic nucleic acid molecules follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μ mol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. **Table II** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μ mol scale can be

done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μ L of 0.11 M = 6.6 μ mol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μ L of 0.25 M = 15 μ mol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μ L of 0.11 M = 13.2 μ mol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μ L of 0.25 M = 30 μ mol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include; detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide 0.05 M in acetonitrile) is used.

Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 μ L of a solution of 1.5 mL *N*-methylpyrrolidinone, 750 μ L TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C. After 1.5 h, the oligomer is quenched with 1.5 M NH₄HCO₃.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 min. The vial is brought

to r.t. TEA•3HF (0.1 mL) is added and the vial is heated at 65 °C for 15 min. The sample is cooled at –20 °C and then quenched with 1.5 M NH₄HCO₃.

For anion exchange desalting of the deprotected oligomer, the TEAB solution was loaded onto a Qiagen 500® anion exchange cartridge (Qiagen Inc.) that was prewashed with 50 mM TEAB (10 mL). After washing the loaded cartridge with 50 mM TEAB (10 mL), the RNA was eluted with 2 M TEAB (10 mL) and dried down to a white powder.

For purification of the trityl-on oligomers, the quenched NH₄HCO₃ solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is detritylated with 0.5% TFA for 13 min. The cartridge is then washed again with water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

Inactive hammerhead enzymatic nucleic acids were synthesized by substituting switching the order of G₅A₆ and substituting a U for A₁₄(numbering from Hertel, K. J., *et al.*, 1992, *Nucleic Acids Res.*, 20, 3252). Inactive enzymatic nucleic acids may also be synthesized by substituting a U for G₅ and a U for A₁₄. In some cases, the sequence of the substrate binding arms were randomized while the overall base composition was maintained.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96 well format, all that is important is the ratio of chemicals used in the reaction.

Enzymatic nucleic acid molecules can be synthesized in two parts and annealed to reconstruct the active enzymatic nucleic acid molecule (Chowrira and Burke, 1992 *Nucleic Acids Res.*, 20, 2835-2840). Enzymatic nucleic acid molecules can also be synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, *Methods Enzymol.* 180, 51). DNAzymes can be synthesized chemically or expressed endogenously *in vivo*, by means of a single stranded DNA vector or equivalent thereof.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No. WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204).

The nucleic acid molecules of the present invention are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). Enzymatic nucleic acids are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Wincott *et al.*, *Supra*, the totality of which is hereby incorporated herein by reference) and are re-suspended in water.

The sequences of the nucleic acid molecules that are chemically synthesized, useful in this study, are shown in **Tables V-VII**. Those in the art will recognize that these sequences are representative only of many more such sequences where the enzymatic portion of the enzymatic nucleic acid (all but the binding arms) is altered to affect activity. The nucleic acid sequences listed in **Tables V-VII** may be formed of ribonucleotides or other nucleotides or non-nucleotides. Such nucleic acid molecules with enzymatic activity are equivalent to the enzymatic nucleic acid molecules described specifically in the tables.

Optimizing Activity of the nucleic acid molecules of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) that prevent their degradation by serum ribonucleases may increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, US Patent No. 5,334,711; and Burgin *et al.*, *supra*; all of these describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules herein). Modifications which enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical

requirements are desired. (All these publications are hereby incorporated by reference herein).

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992, *TIBS*, 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al.*, *International Publication* PCT No. WO 92/07065; Perrault *et al.* *Nature*, 1990, 344, 565-568; Pieken *et al.* *Science*, 1991, 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman *et al.* *International Publication* PCT No. WO 93/15187; Sproat, *US Patent* No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, *International PCT publication* No. WO 97/26270; Beigelman *et al.*, *US Patent* No. 5,716,824; Usman *et al.*, *US patent* No. 5,627,053; Woolf *et al.*, *International PCT Publication* No. WO 98/13526; Thompson *et al.*, *USSN* 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into enzymatic nucleic acids without inhibiting catalysis, and are incorporated by reference herein.

In view of such teachings, similar modifications can be used as described herein to modify the nucleic acid molecules of the instant invention.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorothioate, and/or 5'-methylphosphonate linkages improves stability, too many of these modifications may cause some toxicity. Therefore when designing nucleic acid molecules the amount of these internucleotide linkages should be

minimized. The reduction in the concentration of these linkages should lower toxicity resulting in increased efficacy and higher specificity of these molecules.

Nucleic acid molecules having chemical modifications that maintain or enhance activity are provided. Such nucleic acid is also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or *in vivo* the activity may not be significantly lowered. Therapeutic nucleic acid molecules delivered exogenously must optimally be stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Clearly, nucleic acid molecules must be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211,3-19 (incorporated by reference herein) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

Use of these the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple antisense or enzymatic nucleic acid molecules targeted to different genes, nucleic acid molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations of molecules (including different motifs) and/or other chemical or biological molecules). The treatment of patients with nucleic acid molecules may also include combinations of different types of nucleic acid molecules.

Therapeutic nucleic acid molecules (e.g., enzymatic nucleic acid molecules) delivered exogenously must optimally be stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Clearly, these nucleic acid molecules must be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

By "enhanced enzymatic activity" is meant to include activity measured in cells and/or *in vivo* where the activity is a reflection of both catalytic activity and enzymatic nucleic acid stability. In this invention, the product of these properties is increased or not significantly (less than 10 fold) decreased *in vivo* compared to an all RNA enzymatic nucleic acid or all DNA enzyme.

In yet another preferred embodiment, nucleic acid catalysts having chemical modifications which maintain or enhance enzymatic activity is provided. Such nucleic acid is also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or *in vivo* the activity may not be significantly lowered. As exemplified herein such enzymatic nucleic acids are useful in a cell and/or *in vivo* even if activity over all is reduced 10 fold (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Such enzymatic nucleic acids herein are said to "maintain" the enzymatic activity of an all RNA enzymatic nucleic acid.

In another aspect the nucleic acid molecules comprise a 5' and/or a 3'-cap structure.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see for example Wincott *et al.*, WO 97/26270, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminus (3'-cap) or may be present on both terminus. In non-limiting examples: the 5'-cap is selected from the group comprising inverted abasic residue (moiety), 4',5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide, 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety (for more details see Wincott *et al.*, International PCT publication No. WO 97/26270, incorporated by reference herein). In yet another preferred embodiment the 3'-cap is selected from a group comprising, 4',5'-methylene nucleotide; 1-

(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein). By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino, or SH. The term also includes alkenyl groups which are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂, halogen, N(CH₃)₂, amino, or SH. The term "alkyl" also includes alkynyl groups which have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or

unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino or SH.

Such alkyl groups may also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group which has at least one ring having a conjugated p electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra* all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*,

ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090; Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases may be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

In a preferred embodiment, the invention features modified enzymatic nucleic acids with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39. These references are hereby incorporated by reference herein.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, (for more details see Wincott *et al.*, International PCT publication No. WO 97/26270).

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, uracil joined to the 1' carbon of β -D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH₂ or 2'-O- NH₂, which may be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Patent 5,672,695 and Matulic-Adamic *et al.*, WO 98/28317, respectively, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid (*e.g.*, antisense and enzymatic nucleic acid) structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, *e.g.*, to enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Use of these molecules will lead to better treatment of the disease progression by affording the possibility of combination therapies (*e.g.*, multiple enzymatic nucleic acids targeted to different genes, enzymatic nucleic acids coupled with known small molecule inhibitors, or intermittent treatment with combinations of enzymatic nucleic acids (including different enzymatic nucleic acid motifs) and/or other chemical or biological molecules). The treatment of patients with nucleic acid molecules may also include combinations of different types of nucleic acid molecules. Therapies may be devised which include a mixture of enzymatic nucleic acids (including different enzymatic nucleic acid motifs), antisense and/or 2-5A chimera molecules to one or more targets to alleviate symptoms of a disease.

Administration of Nucleic acid molecules

Sullivan *et al.*, PCT WO 94/02595, describes the general methods for delivery of enzymatic nucleic acid molecules. Nucleic acid molecules may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, enzymatic nucleic acids may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination is locally delivered by direct injection or by use of a catheter, infusion pump, stent or other delivery devices such as Alzet® pumps, Medipad® devices. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of enzymatic nucleic acid delivery and administration are provided in Sullivan *et al.*, *supra* and Draper *et al.*, PCT WO93/23569 which have been incorporated by reference herein.

The molecules of the instant invention can be used as pharmaceutical agents. Pharmaceutical agents prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state in a patient.

The negatively charged polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a patient by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a lipid or liposome delivery mechanism, standard protocols for formulation can be followed. The compositions of the present invention may also be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions; suspensions for injectable administration; and the like.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or patient, preferably a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation to reach a target cell (*i.e.*, a cell to which the negatively charged polymer is desired to be delivered to). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include, without limitations: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes expose the desired negatively charged polymers, *e.g.*, nucleic acids, to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug

carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation which can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach may provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as the HCV infected liver cells.

The invention also features the use of a composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al.* *Chem. Rev.* 1995, **95**, 2601-2627; Ishiwata *et al.*, *Chem. Pharm. Bull.* 1995, **43**, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al.*, *Science* 1995, **267**, 1275-1276; Oku *et al.*, 1995, *Biochim. Biophys. Acta*, **1238**, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al.*, *J. Biol. Chem.* 1995, **42**, 24864-24870; Choi *et al.*, International PCT Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392; all of these are incorporated by reference herein). All of these references are incorporated by reference herein.

In addition other cationic molecules may also be utilized to deliver the molecules of the present invention. For example, enzymatic nucleic acid molecules may be conjugated to glycosylated poly(L-lysine) which has been shown to enhance localization of antisense oligonucleotides into the liver (Nakazono *et al.*, 1996, *Hepatology* 23, 1297-1303; Nahato *et al.*, 1997, *Biochem Pharm.* 53, 887-895). Glycosylated poly(L-lysine) may be covalently attached to the enzymatic nucleic acid or be bound to enzymatic nucleic acid through electrostatic interaction.

The present invention also includes compositions prepared for storage or administration which include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985) hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents may be provided. *Id.* at 1449. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents may be used. —

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the present invention may also be administered to a patient in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication may increase the beneficial effects while reducing the presence of side effects.

Alternatively, the enzymatic nucleic acid molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985 *Science* 229, 345; McGarry and Lindquist, 1986 *Proc. Natl. Acad. Sci. USA* 83, 399; Scanlon *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992 *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992 *J. Virol*, 66, 1432-41; Weerasinghe *et al.*, 1991 *J. Virol*, 65, 5531-4; Ojwang *et al.*, 1992 *Proc. Natl. Acad. Sci. USA* 89, 10802-6; Chen *et al.*, 1992 *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science* 247, 1222-1225; Thompson *et al.*, 1995 *Nucleic Acids Res.* 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45; all of the references are hereby incorporated in their totality by reference herein). Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate

DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by an enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 94/02595; Ohkawa *et al.*, 1992 *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993 *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994 *J. Biol. Chem.* 269, 25856; all of the references are hereby incorporated in their totality by reference herein).

In another aspect of the invention, enzymatic nucleic acid molecules that cleave target molecules are expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Enzymatic nucleic acid molecule expressing viral vectors could be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant vectors capable of expressing the enzymatic nucleic acid molecules are delivered as described above, and persist in target cells. Alternatively, viral vectors may be used that provide for transient expression of enzymatic nucleic acid molecules. Such vectors might be repeatedly administered as necessary. Once expressed, the enzymatic nucleic acid molecules cleave the target mRNA. The active enzymatic nucleic acid molecule contains an enzymatic center or core equivalent to those in the examples, and binding arms able to bind target nucleic acid molecules such that cleavage at the target site occurs. Other sequences may be present which do not interfere with such cleavage. Delivery of enzymatic nucleic acid molecule expressing vectors could be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features, an expression vector comprising nucleic acid sequence encoding at least one of the nucleic acid catalyst of the instant invention is disclosed. The nucleic acid sequence encoding the nucleic acid catalyst of the instant invention is operable linked in a manner that allows expression of that nucleic acid molecule.

In another aspect the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a

transcription termination region (e.g., eukaryotic pol I, II or III termination region); c) a nucleic acid sequence encoding at least one of the nucleic acid catalyst of the instant invention; and wherein said sequence is operably linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. The vector may optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the nucleic acid catalyst of the invention; and/or an intron (intervening sequences).

Transcription of the nucleic acid molecule sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber et al., 1993, *Methods Enzymol.*, 217, 47-66; Zhou et al., 1990, *Mol. Cell. Biol.*, 10, 4529-37). All of these references are incorporated by reference herein. Several investigators have demonstrated that nucleic acid molecules, such as enzymatic nucleic acids expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet et al., 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang et al., 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen et al., 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu et al., 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier et al., 1992, *EMBO J.*, 11, 4411-8; Lisiewicz et al., 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson et al., 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as enzymatic nucleic acids in cells (Thompson et al., *supra*; Couture and Stinchcomb, 1996, *supra*; Noonberg et al., 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg et al., US Patent No. 5,624,803; Good et al., 1997, *Gene Ther.*, 4, 45; Beigelman et al., International PCT Publication No. WO 96/18736; all of these publications are incorporated by reference herein. The above enzymatic nucleic acid molecule transcription units can be incorporated into a

variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, *supra*).

5 In yet another aspect the invention features an expression vector comprising nucleic acid sequence encoding at least one of the nucleic acid molecules of the invention, in a manner which allows expression of that nucleic acid molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; c) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In another preferred embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; d) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In yet another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region, said intron and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule. In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; e) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said intron, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

Interferons

Type I interferons (IFN) are a class of natural cytokines that includes a family of greater than 25 IFN- α (Pesta, 1986, *Methods Enzymol.* 119, 3-14) as well as IFN- β , and IFN- ω . Although evolutionarily derived from the same gene (Diaz *et al.*, 1994, *Genomics* 22, 540-552), there are many differences in the primary sequence of these molecules, implying an evolutionary divergence in biologic activity. All type I IFN share a common pattern of biologic effects that begin with binding of the IFN to the cell surface receptor (Pfeffer & Strulovici, 1992, Transmembrane secondary messengers for IFN- α/β . In: *Interferon. Principles and Medical Applications.*, S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds. 151-160). Binding is followed by activation of tyrosine kinases, including the Janus tyrosine kinases and the STAT proteins, which leads to the production of several IFN-stimulated gene products (Johnson *et al.*, 1994, *Sci. Am.* 270, 68-75). The IFN-stimulated gene products are responsible for the pleotropic biologic effects of type I IFN, including antiviral, antiproliferative, and immunomodulatory effects, cytokine induction, and HLA class I and class II regulation (Pestka *et al.*, 1987, *Annu. Rev. Biochem* 56, 727). Examples of IFN-stimulated gene products include 2-5-oligoadenylate synthetase (2-5 OAS), β_2 -microglobulin, neopterin, p68 kinases, and the Mx protein (Chebath & Revel, 1992, The 2-5 A system: 2-5 A synthetase, isospecies and functions. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Jr. Fleischmann, T.K. Jr Hughes, G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds., pp. 225-236; Samuel, 1992, The RNA-dependent P1/eIF-2 α protein kinase. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 237-250; Horisberger, 1992, MX protein: function and Mechanism of Action. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 215-224). Although all type I IFN have similar biologic effects, not all the activities are shared by each type I IFN, and, in many cases, the extent of activity varies quite substantially for each IFN subtype (Fish *et al.*, 1989, *J. Interferon Res.* 9, 97-114; Ozes *et al.*, 1992, *J. Interferon Res.* 12, 55-59). More specifically, investigations into the properties of different subtypes of IFN- α and molecular hybrids of IFN- α have shown differences in pharmacologic properties (Rubinstein, 1987, *J. Interferon*

Res. 7, 545-551). These pharmacologic differences may arise from as few as three amino acid residue changes (Lee *et al.*, 1982, *Cancer Res.* 42, 1312-1316).

Eighty-five to 166 amino acids are conserved in the known IFN- α subtypes.

Excluding the IFN- α pseudogenes, there are approximately 25 known distinct IFN- α

subtypes. Pairwise comparisons of these nonallelic subtypes show primary sequence differences ranging from 2% to 23%. In addition to the naturally occurring IFNs, a non-natural recombinant type I interferon known as consensus interferon (CIFN) has been synthesized as a therapeutic compound (Tong *et al.*, 1997, *Hepatology* 26, 747-754).

Interferon is currently in use for at least 12 different indications including infectious and autoimmune diseases and cancer (Borden, 1992, *N. Engl. J. Med.* 326, 1491-1492). For autoimmune diseases IFN has been utilized for treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease. For treatment of cancer IFN has been used alone or in combination with a number of different compounds. Specific types of cancers for which IFN has been used include squamous cell carcinomas, melanomas, hypernephromas, hemangiomas, hairy cell leukemia, and Kaposi's sarcoma. In the treatment of infectious diseases, IFNs increase the phagocytic activity of macrophages and cytotoxicity of lymphocytes and inhibits the propagation of cellular pathogens. Specific indications for which IFN has been used as treatment include: hepatitis B, human papillomavirus types 6 and 11 (i.e. genital warts) (Leventhal *et al.*, 1991, *N Engl J Med* 325, 613-617), chronic granulomatous disease, and hepatitis C virus.

Numerous well controlled clinical trials using IFN-alpha in the treatment of chronic HCV infection have demonstrated that treatment three times a week results in lowering of serum ALT values in approximately 50% (range 40% to 70%) of patients by the end of 6 months of therapy (Davis *et al.*, 1989, *The new England Journal of Medicine* 321, 1501-1506; Marcellin *et al.*, 1991, *Hepatology* 13, 393-397; Tong *et al.*, 1997, *Hepatology* 26, 747-754; Tong *et al.*, *Hepatology* 26, 1640-1645). However, following cessation of interferon treatment, approximately 50% of the responding patients relapsed, resulting in a "durable" response rate as assessed by normalization of serum ALT concentrations of approximately 20 to 25%. In addition, studies that have examined six months of type 1 interferon therapy using changes in HCV RNA values as a clinical endpoint have demonstrated that up to 35% of patients will have a loss of HCV RNA by the end of therapy (Tong *et al.*, 1997, *supra*).

However, as with the ALT endpoint, about 50% of the patients relapse six months following cessation of therapy resulting in a durable virologic response of only 12% (23). Studies that have examined 48 weeks of therapy have demonstrated that the sustained virological response is up to 25%.

5 Pegylated interferons, ie. interferons conjugated with polyethylene glycol (PEG), have demonstrated improved characteristics over interferon. Advantages incurred by PEG conjugation can include an improved pharmacokinetic profile compared to interferons lacking PEG, thus imparting more convenient dosing regimes, improved tolerance, and improved antiviral efficacy. Such improvements have been demonstrated in clinical studies of both
10 polyethylene glycol interferon alfa-2a (PEGASYS, Roche) and polyethylene glycol interferon alfa-2b (VIRAIFERON PEG, PEG-INTRON, Enzon/Schering Plough).

Enzymatic nucleic acid molecules in combination with interferons and polyethylene glycol interferons have the potential to improve the effectiveness of treatment of HCV or any of the other indications discussed above. Enzymatic nucleic acid molecules targeting RNAs
15 associated with diseases such as infectious diseases, autoimmune diseases, and cancer, can be used individually or in combination with other therapies such as interferons and polyethylene glycol interferons and to achieve enhanced efficacy.

Examples

20 The following are non-limiting examples showing the selection, isolation, synthesis and activity of enzymatic nucleic acids of the instant invention.

The following examples demonstrate the use of enzymatic nucleic acid molecules that cleave HCV RNA. The methods described herein represent a scheme by which nucleic acid molecules can be derived that cleave other RNA targets required for HCV replication.

Example 1: Identification of Potential Enzymatic nucleic acid molecules Cleavage Sites in 25 HCV RNA

The sequence of HCV RNA was screened for accessible sites using a computer folding algorithm. Regions of the mRNA that did not form secondary folding structures and

contained potential hammerhead and/or hairpin enzymatic nucleic acid cleavage sites were identified. The sequences of these cleavage sites are shown in **Tables III-V**.

Example 2: Selection of Enzymatic nucleic acid molecules Cleavage Sites in HCV RNA

Enzymatic nucleic acid target sites were chosen by analyzing sequences of Human HCV (Genbank accession Nos: D11168 , D50483.1, L38318 and S82227) and prioritizing the sites on the basis of folding. Enzymatic nucleic acid molecules are designed that could bind each target and are individually analyzed by computer folding (Christoffersen *et al.*, 1994 *J. Mol. Struc. Theochem*, 311, 273; Jaeger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA*, 86, 7706) to assess whether the enzymatic nucleic acid molecules sequences fold into the appropriate secondary structure. Those enzymatic nucleic acid molecules with unfavorable intramolecular interactions between the binding arms and the catalytic core can be eliminated from consideration. As noted below, varying binding arm lengths can be chosen to optimize activity. Generally, at least 4 bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Example 3: Chemical Synthesis and Purification of Enzymatic nucleic acids

Enzymatic nucleic acid molecules can be designed to anneal to various sites in the RNA message. The binding arms of the enzymatic nucleic acid molecules are complementary to the target site sequences described above. The enzymatic nucleic acid molecules can be chemically synthesized using, for example, RNA syntheses such as those described above and those described in Usman *et al.*, (1987 *J. Am. Chem. Soc.*, 109, 7845), Scaringe *et al.*, (1990 *Nucleic Acids Res.*, 18, 5433) and Wincott *et al.*, *supra*. Such methods make use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. The average stepwise coupling yields are typically >98%. Enzymatic nucleic acid molecules can be modified to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992 *TIBS* 17, 34).

Enzymatic nucleic acid molecules can also be synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, *Methods Enzymol.* 180, 51). Enzymatic nucleic acid molecules can be purified by gel electrophoresis using known methods, or can be purified by high pressure liquid chromatography (HPLC; See Wincott *et al.*, *supra*; the totality of which is hereby incorporated herein by reference), and are

resuspended in water. The sequences of chemically synthesized enzymatic nucleic acid constructs are shown below in **Tables V and VI**. The antisense nucleic acid molecules shown in **Table VII** were chemically synthesized.

Inactive enzymatic nucleic acid molecules, for example inactive hammerhead enzymatic nucleic acids, can be synthesized by substituting the order of G5A6 and substituting a U for A14 (numbering from Hertel et al., 1992 Nucleic Acids Res., 20, 3252).

Example 4: Enzymatic Nucleic Acid Cleavage of HCV RNA Target *in vitro*

Enzymatic nucleic acid molecules targeted to the HCV are designed and synthesized as described above. These enzymatic nucleic acid molecules can be tested for cleavage activity *in vitro*, for example using the following procedure. The target sequences and the nucleotide location within the HCV are given in **Table V**.

Cleavage Reactions: Full-length or partially full-length, internally-labeled target RNA for enzymatic nucleic acid molecule cleavage assay is prepared by *in vitro* transcription in the presence of [α - 32 P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as substrate RNA without further purification. Alternately, substrates are 5'- 32 P-end labeled using T4 polynucleotide kinase enzyme. Assays are performed by pre-warming a 2X concentration of purified enzymatic nucleic acid molecule in enzymatic nucleic acid molecule cleavage buffer (50 mM Tris-HCl, pH 7.5 at 37°C, 10 mM MgCl₂) and the cleavage reaction was initiated by adding the 2X enzymatic nucleic acid molecule mix to an equal volume of substrate RNA (maximum of 1-5 nM) that was also pre-warmed in cleavage buffer. As an initial screen, assays are carried out for 1 hour at 37°C using a final concentration of either 40 nM or 1 mM enzymatic nucleic acid molecule, *i.e.*, enzymatic nucleic acid molecule excess. The reaction is quenched by the addition of an equal volume of 95% formamide, 20 mM EDTA, 0.05% bromophenol blue and 0.05% xylene cyanol after which the sample is heated to 95°C for 2 minutes, quick chilled and loaded onto a denaturing polyacrylamide gel. Substrate RNA and the specific RNA cleavage products generated by enzymatic nucleic acid molecule cleavage are visualized on an autoradiograph of the gel. The percentage of cleavage is determined by Phosphor Imager[®] quantitation of bands representing the intact substrate and the cleavage products.

Alternatively, enzymatic nucleic acid molecules and substrates were synthesized in 96-well format using 0.2μmol scale. Substrates were 5'-³²P labeled and gel purified using 7.5% polyacrylamide gels, and eluting into water. Assays were done by combining trace substrate with 500nM enzymatic nucleic acid or greater, and initiated by adding final concentrations of 40mM Mg²⁺, and 50mM Tris-Cl pH 8.0. For each enzymatic nucleic acid/substrate combination a control reaction was done to ensure cleavage was not the result of non-specific substrate degradation. A single three hour time point was taken and run on a 15% polyacrylamide gel to assess cleavage activity. Gels were dried and scanned using a Molecular Dynamics Phosphorimager and quantified using Molecular Dynamics ImageQuant software. Percent cleaved was determined by dividing values for cleaved substrate bands by full-length (uncleaved) values plus cleaved values and multiplying by 100 (%cleaved=[C/(U+C)]*100). In vitro cleavage data of enzymatic nucleic acid molecules targeting plus and minus strand HCV RNA is shown in **Table VIII**.

Example 5: Inhibition of Luciferase Activity Using HCV Targeting Enzymatic nucleic acids in OST7 Cells

The capability of enzymatic nucleic acids to inhibit HCV RNA intracellularly was tested using a dual reporter system that utilizes both firefly and Renilla luciferase (**Figure 6**). The enzymatic nucleic acids targeted to the 5' HCV UTR region, which when cleaved, would prevent the translation of the transcript into luciferase.

Synthesis of Stabilized Enzymatic nucleic acids

Enzymatic nucleic acids were designed to target 15 sites within the 5'UTR of the HCV RNA (**Figure 7**) and synthesized as previously described, except that all enzymatic nucleic acids contain two 2'-amino uridines. All enzymatic nucleic acid and paired control sequences for targeted sites used in various examples herein are shown in **Table VI**.

Reporter plasmids

The T7/HCV/firefly luciferase plasmid (HCVT7C₁₋₃₄₁, genotype 1a) was graciously provided by Aleem Siddiqui (University of Colorado Health Sciences Center, Denver, CO). The T7/HCV/firefly luciferase plasmid contains a T7 bacteriophage promoter upstream of the

HCV 5'UTR (nucleotides 1-341)/firefly luciferase fusion DNA. The Renilla luciferase control plasmid (pRLSV40) was purchased from PROMEGA.

Luciferase assay

Dual luciferase assays were carried out according to the manufacturer's instructions (PROMEGA) at 4 hours after co-transfection of reporter plasmids and enzymatic nucleic acids. All data is shown as the average ratio of HCV/firefly luciferase luminescence over Renilla luciferase luminescence as determined by triplicate samples \pm SD.

Cell culture and transfections

OST7 cells were maintained in Dulbecco's modified Eagle's medium (GIBCO BRL) supplemented with 10% fetal calf serum, L-glutamine (2 mM) and penicillin/streptomycin. For transfections, OST7 cells were seeded in black-walled 96-well plates (Packard) at a density of 12,500 cells/well and incubated at 37°C under 5% CO₂ for 24 hours. Co-transfection of target reporter HCV7C (0.8 μ g/mL), control reporter pRLSV40, (1.2 μ g/mL) and enzymatic nucleic acid, (50 - 200 nM) was achieved by the following method: a 5X mixture of HCV7C (4 μ g/mL), pRLSV40 (6 μ g/mL) enzymatic nucleic acid (250 - 1000 nM) and cationic lipid (28.5 μ g/mL) was made in 150 μ L of OPTI-MEM (GIBCO BRL) minus serum. Reporter/enzymatic nucleic acid/lipid complexes were allowed to form for 20 min at 37°C under 5% CO₂. Medium was aspirated from OST7 cells and replaced with 120 μ L of OPTI-MEM (GIBCO BRL) minus serum, immediately followed by the addition of 30 μ L of 5X reporter/enzymatic nucleic acid/lipid complexes. Cells were incubated with complexes for 4 hours at 37°C under 5% CO₂.

IC₅₀ determinations for dose response curves

Apparent IC₅₀ values were calculated by linear interpolation. The apparent IC₅₀ is 1/2 the maximal response between the two consecutive points in which approximately 50% inhibition of HCV/luciferase expression is observed on the dose curve.

Quantitation of RNA Samples

Total RNA from transfected cells was purified using the Qiagen RNeasy 96 procedure including a DNase I treatment according to the manufacturer's instructions. Real time RT-PCR (Taqman assay) was performed on purified RNA samples using separate primer/probe sets specific for either firefly or Renilla luciferase RNA. Firefly luciferase primers and probe were upper (5'-CGGTCGGTAAAGTTGTTCCATT-3'), lower (5'-CCTCTGACACATAATTCGCCTCT-3'), and probe (5'-FAM-TGAAGCGAAGGTTGTGGATCTGGATACC-TAMRA-3'), and Renilla luciferase primers and probe were upper (5'-GTTTATTGAATCGGACCCAGGAT-3'), lower (5'-AGGTGCATCTTCTTGCGAAAA-3'), and probe (5'-FAM-CTTTTCCAATGCTATTGTTGAAGGTGCCAA-TAMRA-3'), both sets of primers and probes were purchased from Integrated DNA Technologies. RNA levels were determined from a standard curve of amplified RNA purified from a large-scale transfection. RT minus controls established that RNA signals were generated from RNA and not residual plasmid DNA. RT-PCR conditions were: 30 min at 48°C, 10 min at 95°C, followed by 40 cycles of 15 sec at 95°C and 1 min at 60°C. Reactions were performed on an ABI Prism 7700 sequence detector. Levels of firefly luciferase RNA were normalized to the level of Renilla luciferase RNA present in the same sample. Results are shown as the average of triplicate treatments \pm SD.

Example 6: Inhibition of HCV 5'UTR-luciferase expression by synthetic stabilized enzymatic nucleic acids

The primary sequence of the HCV 5'UTR and characteristic secondary structure (**Figure 7**) is highly conserved across all HCV genotypes, thus making it a very attractive target for enzymatic nucleic acid-mediated cleavage. Enzymatic hammerhead nucleic acids, as a generally shown in **Figure 8** and **Table VI** (RPI 12249-12254, 12257-12265) were designed and synthesized to target 15 of the most highly conserved sites in the 5'UTR of HCV RNA. These synthetic enzymatic nucleic acids were stabilized against nuclease degradation by the addition of modifications such as 2'-O-methyl nucleotides, 2'-amino-uridines at U4 and U7 core positions, phosphorothioate linkages, and a 3'-inverted abasic cap.

In order to mimic cytoplasmic transcription of the HCV genome, OST7 cells were transfected with a target reporter plasmid containing a T7 bacteriophage promoter upstream of

a HCV 5'UTR/firefly luciferase fusion gene. Cytoplasmic expression of the target reporter is facilitated by high levels of T7 polymerase expressed in the cytoplasm of OST7 cells. Co-transfection of target reporter HCVT7C₁₋₃₄₁ (firefly luciferase), control reporter pRLSV40 (Renilla luciferase) and enzymatic nucleic acid was carried out in the presence of cationic lipid. To determine the background level of luciferase activity, applicant used a control enzymatic nucleic acid that targets an irrelevant, non-HCV sequence. Transfection of reporter plasmids in the presence of this irrelevant control enzymatic nucleic acid (ICR) resulted in a slight decrease of reporter expression when compared to transfection of reporter plasmids alone. Therefore, the ICR was used to control for non-specific effects on reporter expression during treatment with HCV specific enzymatic nucleic acids. Renilla luciferase expression from the pRLSV40 reporter was used to normalize for transfection efficiency and sample recovery.

Of the 15 amino-modified hammerhead enzymatic nucleic acids tested, 12 significantly inhibited HCV/luciferase expression ($> 45\%$, $P < 0.05$) as compared to the ICR (**Figure 9A**). These data suggest that most of the HCV 5'UTR sites targeted here are accessible to enzymatic nucleic acid binding and subsequent RNA cleavage. To investigate further the enzymatic nucleic acid-dependent inhibition of HCV/luciferase activity, hammerhead enzymatic nucleic acids designed to cleave after sites 79, 81, 142, 192, 195, 282 or 330 of the HCV 5'UTR were selected for continued study because their anti-HCV activity was the most efficacious over several experiments. A corresponding attenuated core (AC) control was synthesized for each of the 7 active enzymatic nucleic acids (**Table VI**). Each paired AC control contains similar nucleotide composition to that of its corresponding active enzymatic nucleic acid however, due to scrambled binding arms and changes to the catalytic core, lacks the ability to bind or catalyze the cleavage of HCV RNA. Treatment of OST7 cells with enzymatic nucleic acids designed to cleave after sites 79, 81, 142, 195 or 330 resulted in significant inhibition of HCV/luciferase expression (65%, 50%, 50%, 80% and 80%, respectively) when compared to HCV/luciferase expression in cells treated with corresponding ACs, $P < 0.05$ (**Figure 9B**). It should be noted that treatment with either the ICR or ACs for sites 79, 81, 142 or 192 caused a greater reduction of HCV/luciferase expression than treatment with ACs for sites 195, 282 or 330. The observed differences in HCV/luciferase expression after treatment with ACs most likely represents the range of

activity due to non-specific effects of oligonucleotide treatment and/or differences in base composition. Regardless of differences in HCV/luciferase expression levels observed as a result of treatment with ACs, active enzymatic nucleic acids designed to cleave after sites 79, 81, 142, 195, or 330 demonstrated similar and potent anti-HCV activity (**Figure 9B**).

5 Example 7: Synthetic stabilized enzymatic nucleic acids inhibit HCV/luciferase expression in a concentration-dependent manner

In order to characterize enzymatic nucleic acid efficacy in greater detail, these same 5 lead hammerhead enzymatic nucleic acids were tested for their ability to inhibit HCV/luciferase expression over a range of enzymatic nucleic acid concentrations (0 nM - 100 nM). For constant transfection conditions, the total concentration of nucleic acid was maintained at 100 nM for all samples by mixing the active enzymatic nucleic acid with its corresponding AC. Moreover, mixing of active enzymatic nucleic acid and AC maintains the lipid to nucleic acid charge ratio. A concentration-dependent inhibition of HCV/luciferase expression was observed after treatment with each of the 5 enzymatic nucleic acids (**Figures 10A-E**). By linear interpolation, the enzymatic nucleic acid concentration resulting in 50% inhibition (apparent IC_{50}) of HCV/luciferase expression ranged from 40 - 215 nM. The two most efficacious enzymatic nucleic acids were those designed to cleave after sites 195 or 330 with apparent IC_{50} values of 46 nM and 40 nM, respectively (**Figures 10D and E**).

15 Example 8: An enzymatic nucleic acid mechanism is required for the observed inhibition of HCV/luciferase expression

To confirm that an enzymatic nucleic acid mechanism of action was responsible for the observed inhibition of HCV/luciferase expression, paired binding-arm attenuated core (BAC) controls (RPI 15291 and 15294) were synthesized for direct comparison to enzymatic nucleic acids targeting sites 195 (RPI 12252) and 330 (RPI 12254). Paired BACs can specifically bind HCV RNA but are unable to promote RNA cleavage because of changes in the catalytic core and, thus, can be used to assess inhibition due to binding alone. Also included in this comparison were paired SAC controls (RPI 15292 and 15295) that contain scrambled binding arms and attenuated catalytic cores, and so lack the ability to bind the target RNA or to catalyze target RNA cleavage.

Enzymatic nucleic acid cleavage of target RNA should result in both a lower level of HCV/luciferase RNA and a subsequent decrease in HCV/luciferase expression. In order to analyze target RNA levels, a reverse transcriptase/polymerase chain reaction (RT-PCR) assay was employed to quantify HCV/luciferase RNA levels. Primers were designed to amplify the luciferase coding region of the HCV 5'UTR/luciferase RNA. This region was chosen because HCV-targeted enzymatic nucleic acids that might co-purify with cellular RNA would not interfere with RT-PCR amplification of the luciferase RNA region. Primers were also designed to amplify the Renilla luciferase RNA so that Renilla RNA levels could be used to control for transfection efficiency and sample recovery.

OST7 cells were treated with active enzymatic nucleic acids designed to cleave after sites 195 or 330, paired SACs, or paired BACs. Treatment with enzymatic nucleic acids targeting site 195 or 330 resulted in a significant reduction of HCV/luciferase RNA when compared to their paired SAC controls ($P < 0.01$). In this experiment the site 195 enzymatic nucleic acid was more efficacious than the site 330 enzymatic nucleic acid (**Figure 11A**). Treatment with paired BACs that target site 195 or 330 did not reduce HCV/luciferase RNA when compared to the corresponding SACs, thus confirming that the ability to bind alone does not result in a reduction of HCV/luciferase RNA.

To confirm that enzymatic nucleic acid-mediated cleavage of target RNA is necessary for inhibition of HCV/luciferase expression, HCV/luciferase activity was determined in the same experiment. As expected, significant inhibition of HCV/luciferase expression was observed after treatment with active enzymatic nucleic acids when compared to paired SACs (**Figure 11B**). Importantly, treatment with paired BACs did not inhibit HCV/luciferase expression, thus confirming that the ability to bind alone is also not sufficient to inhibit translation. As observed in the RNA assay, the site 195 enzymatic nucleic acid was more efficacious than the site 330 enzymatic nucleic acid in this experiment. However, a correlation between enzymatic nucleic acid-mediated HCV RNA reduction and inhibition of HCV/luciferase translation was observed for enzymatic nucleic acids to both sites. The reduction in target RNA and the necessity for an active enzymatic nucleic acid catalytic core confirm that a enzymatic nucleic acid mechanism is required for the observed reduction in HCV/luciferase protein activity in cells treated with site 195 or site 330 enzymatic nucleic acids.

Example 9: Zinzyme Inhibition of chimeric HCV/Poliovirus replication

During HCV infection, viral RNA is present as a potential target for enzymatic nucleic acid cleavage at several processes: un-coating, translation, RNA replication and packaging. Target RNA may be more or less accessible to enzymatic nucleic acid cleavage at any one of these steps. Although the association between the HCV initial ribosome entry site (IRES) and the translation apparatus is mimicked in the HCV 5'UTR/luciferase reporter system, these other viral processes are not represented in the OST7 system. The resulting RNA/protein complexes associated with the target viral RNA are also absent. Moreover, these processes may be coupled in an HCV-infected cell which could further impact target RNA accessibility. Therefore, applicant tested whether enzymatic nucleic acids designed to cleave the HCV 5'UTR could effect a replicating viral system.

Recently, Lu and Wimmer characterized a HCV-poliovirus chimera in which the poliovirus IRES was replaced by the IRES from HCV (Lu & Wimmer, 1996, Proc. Natl. Acad. Sci. USA. 93, 1412-1417). Poliovirus (PV) is a positive strand RNA virus like HCV, but unlike HCV is non-enveloped and replicates efficiently in cell culture. The HCV-PV chimera expresses a stable, small plaque phenotype relative to wild type PV.

The following enzymatic nucleic acid molecules (zinzymes) were synthesized and tested for replicative inhibition of an HCV/Poliovirus chimera: RPI 18763, RPI 18812, RPI 18749, RPI 18765, RPI 18792, and RPI 18814 (**Table V**). A scrambled attenuated core enzymatic nucleic acid, RPI 18743, was used as a control.

HeLa cells were infected with the HCV-PV chimera for 30 minutes and immediately treated with enzymatic nucleic acid. HeLa cells were seeded in U-bottom 96-well plates at a density of 9000-10,000 cells/well and incubated at 37°C under 5% CO₂ for 24 h. Transfection of nucleic acid (200 nM) was achieved by mixing of 10X nucleic acid (2000 nM) and 10X of a cationic lipid (80 µg/ml) in DMEM (Gibco BRL) with 5% fetal bovine serum (FBS). Nucleic acid/lipid complexes were allowed to incubate for 15 minutes at 37°C under 5% CO₂. Medium was aspirated from cells and replaced with 80 µl of DMEM (Gibco BRL) with 5% FBS serum, followed by the addition of 20 µls of 10X complexes. Cells were incubated with complexes for 24 hours at 37°C under 5% CO₂.

The yield of HCV-PV from treated cells was quantified by plaque assay. The plaque assays were performed by diluting virus samples in serum-free DMEM (Gibco BRL) and applying 100 µl to HeLa cell monolayers (~80% confluent) in 6-well plates for 30 minutes. Infected monolayers were overlaid with 3 ml 1.2% agar (Sigma) and incubated at 37°C under 5% CO₂. Two or three days later the overlay was removed, monolayers were stained with 1.2% crystal violet, and plaque forming units were counted. The results for the zinzyme inhibition of HCV-PV replication are shown in **Figure 16**.

Example 10: Antisense inhibition of chimeric HCV/Poliovirus replication

Antisense nucleic acid molecules (RPI 17501 and RPI 17498, **Table VII**) were tested for replicative inhibition of an HCV/Poliovirus chimera compared to scrambled controls. An antisense nucleic acid molecule is a non-enzymatic nucleic acid molecule that binds to target RNA by means of RNA-RNA or RNA-DNA or RNA-PNA (protein nucleic acid; Egholm *et al.*, 1993 *Nature* 365, 566) interactions and alters the activity of the target RNA (for a review, see Stein and Cheng, 1993 *Science* 261, 1004 and Woolf *et al.*, US patent No. 5,849,902). Typically, antisense molecules are complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule may bind to substrate such that the substrate molecule forms a loop, and/or an antisense molecule may bind such that the antisense molecule forms a loop. Thus, the antisense molecule may be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule may be complementary to a target sequence or both. For a review of current antisense strategies, see Schmajuk *et al.*, 1999, *J. Biol. Chem.*, 274, 21783-21789, Delihis *et al.*, 1997, *Nature*, 15, 751-753, Stein *et al.*, 1997, *Antisense N. A. Drug Dev.*, 7, 151, Crooke, 2000, *Methods Enzymol.*, 313, 3-45; Crooke, 1998, *Biotech. Genet. Eng. Rev.*, 15, 121-157, Crooke, 1997, *Ad. Pharmacol.*, 40, 1-49. In addition, antisense DNA can be used to target RNA by means of DNA-RNA interactions, thereby activating RNase H, which digests the target RNA in the duplex. The antisense oligonucleotides can comprise one or more RNase H activating region, which is capable of activating RNase H cleavage of a target RNA. Antisense DNA can be synthesized chemically or expressed via the use of a single stranded DNA expression vector or equivalent thereof. Additionally, antisense molecules can be used in combination with the enzymatic nucleic acid molecules of the instant invention.

A “RNase H activating region” is a region (generally greater than or equal to 4-25 nucleotides in length, preferably from 5-11 nucleotides in length) of a nucleic acid molecule

capable of binding to a target RNA to form a non-covalent complex that is recognized by cellular RNase H enzyme (see for example Arrow *et al.*, US 5,849,902; Arrow *et al.*, US 5,989,912). The RNase H enzyme binds to the nucleic acid molecule-target RNA complex and cleaves the target RNA sequence. The RNase H activating region comprises, for example, phosphodiester, phosphorothioate (preferably at least four of the nucleotides are phosphorothioate substitutions; more specifically, 4-11 of the nucleotides are phosphorothioate substitutions); phosphorodithioate, 5'-thiophosphate, or methylphosphonate backbone chemistry or a combination thereof. In addition to one or more backbone chemistries described above, the RNase H activating region can also comprise a variety of sugar chemistries. For example, the RNase H activating region can comprise deoxyribose, arabinose, fluoroarabinose or a combination thereof, nucleotide sugar chemistry. Those skilled in the art will recognize that the foregoing are non-limiting examples and that any combination of phosphate, sugar and base chemistry of a nucleic acid that supports the activity of RNase H enzyme is within the scope of the definition of the RNase H activating region and the instant invention.

HeLa cells were infected with the HCV-PV chimera for 30 minutes and immediately treated with antisense nucleic acid. HeLa cells were seeded in U-bottom 96-well plates at a density of 9000-10,000 cells/well and incubated at 37°C under 5% CO₂ for 24 h. Transfection of nucleic acid (200 nM) was achieved by mixing of 10X nucleic acid (2000 nM) and 10X of a cationic lipid (80 µg/ml) in DMEM (Gibco BRL) with 5% fetal bovine serum (FBS). Nucleic acid/lipid complexes were allowed to incubate for 15 minutes at 37°C under 5% CO₂. Medium was aspirated from cells and replaced with 80 µl of DMEM (Gibco BRL) with 5% FBS serum, followed by the addition of 20 µl of 10X complexes. Cells were incubated with complexes for 24 hours at 37°C under 5% CO₂.

The yield of HCV-PV from treated cells was quantified by plaque assay. The plaque assays were performed by diluting virus samples in serum-free DMEM (Gibco BRL) and applying 100 µl to HeLa cell monolayers (~80% confluent) in 6-well plates for 30 minutes. Infected monolayers were overlaid with 3 ml 1.2% agar (Sigma) and incubated at 37°C under 5% CO₂. Two or three days later the overlay was removed, monolayers were stained with 1.2% crystal violet, and plaque forming units were counted. The results for the antisense inhibition of HCV-PV are shown in **Figure 17**.

Example 11: Nucleic acid Inhibition of Chimeric HCV/PV in combination with Interferon

One of the limiting factors in interferon (IFN) therapy for chronic HCV are the toxic side effects associated with IFN. Applicant has reasoned that lowering the dose of IFN needed may reduce these side effects. Applicant has previously shown that enzymatic nucleic acid molecules targeting HCV RNA have a potent antiviral effect against replication of an HCV-poliovirus (PV) chimera (Macejak *et al.*, 2000, *Hepatology*, 31, 769-776). In order to determine if the antiviral effect of type 1 IFN could be improved by the addition of anti-HCV enzymatic nucleic acid treatment, a dose response (0 U/ml to 100 U/ml) with IFN alfa 2a or IFN alfa 2b was performed in HeLa cells in combination with 200 nM site 195 anti-HCV enzymatic nucleic acid (RPI 13919) or enzymatic nucleic acid control (SAC) treatment. The SAC control (RPI 17894) is a scrambled binding arm, attenuated core version of the site 195 enzymatic nucleic acid (RPI 13919). IFN dose responses were performed with different pretreatment regimes to find the dynamic range of inhibition in this system. In these studies, HeLa cells were used instead of HepG2 because of more efficient enzymatic nucleic acid delivery (Macejak *et al.*, 2000, *Hepatology*, 31, 769-776).

Cells and Virus

HeLa cells were maintained in DMEM (BioWhittaker, Walkersville, MD) supplemented with 5% fetal bovine serum. A cloned DNA copy of the HCV-PV chimeric virus was a gift of Dr. Eckard Wimmer (NYU, Stony Brook, NY). An RNA version was generated by in vitro transcription and transfected into HeLa cells to produce infectious virus (Lu and Wimmer, 1996, PNAS USA., 93, 1412-1417).

Enzymatic nucleic acid Synthesis

Nuclease resistant enzymatic nucleic acids and control oligonucleotides containing 2'-O-methyl-nucleotides, 2'-deoxy-2'-C-allyl uridine, a 3'-inverted abasic cap, and phosphorothioate linkages were chemically synthesized. The anti-HCV enzymatic nucleic acid (RPI 13919) targeting cleavage after nucleotide 195 of the 5' UTR of HCV is shown in **Table V**. Attenuated core controls have nucleotide changes in the core sequence that greatly diminished the enzymatic nucleic acid's cleavage activity. The attenuated controls either contain scrambled binding arms (referred to as SAC, RPI 18743) or maintain binding arms (BAC, RPI 17894) capable of binding to the HCV RNA target.

Enzymatic nucleic acid Delivery

A cationic lipid was used as a cytofectin agent. HeLa cells were seeded in 96-well plates at a density of 9000-10,000 cells/well and incubated at 37°C under 5% CO₂ for 24 h. Transfection of enzymatic nucleic acid or control oligonucleotides (200 nM) was achieved by mixing 10X enzymatic nucleic acid or control oligonucleotides (2000 nM) with 10X RPI.9778 (80 µg/ml) in DMEM containing 5% fetal bovine serum (FBS) in U-bottom 96-well plates to make 5X complexes. Enzymatic nucleic acid/lipid complexes were allowed to incubate for 15 min at 37°C under 5% CO₂. Medium was aspirated from cells and replaced with 80 µl of DMEM (Gibco BRL) containing 5% FBS serum, followed by the addition of 20 µl of 5X complexes. Cells were incubated with complexes for 24 h at 37°C under 5% CO₂.

Interferon/Enzymatic nucleic acid Combination Treatment

Interferon alfa 2a (Roferon®) was purchased from Roche Bioscience (Palo Alto, CA). Interferon alfa 2b (Intron A®) was purchased from Schering-Plough Corporation (Madison, NJ). Consensus interferon (interferon-alfa-con 1) was a generous gift of Amgen, Inc. (Thousand Oaks, CA). For the basis of comparison, the manufacturers' specified units were used in the studies reported here; however, the manufacturers' unit definitions of these three IFN preparations are not necessarily the same. Nevertheless, since clinical dosing is based on the manufacturers' specified units, a direct comparison based on these units has relevance to clinical therapeutic indices. HeLa cells were seeded (10,000 cells per well) and incubated at 37°C under 5% CO₂ for 24 h. Cells were then pre-treated with interferon in complete media (DMEM + 5% FBS) for 4 h and then infected with HCV-PV at a multiplicity of infection (MOI) = 0.1 for 30 min. The viral inoculum was then removed and enzymatic nucleic acid or attenuated control (SAC or BAC) was delivered with the cytofectin formulation (8 µg/ml) in complete media for 24 h as described above. Where indicated for enzymatic nucleic acid dose response studies, active enzymatic nucleic acid was mixed with SAC to maintain a 200 nM total oligonucleotide concentration and the same lipid charge ratio. After 24 h, cells were lysed to release virus by three cycles of freeze/thaw. Virus was quantified by plaque assay and viral yield is reported as mean plaque forming units per ml (pfu/ml) + SD. All experiments

were repeated at least twice and the trends in the results reported were reproducible. Significance levels (P values) were determined by the Student's test.

Plaque Assay

Virus samples were diluted in serum-free DMEM and 100 μ l applied to Vero cell monolayers (~80% confluent) in 6-well plates for 30 min. Infected monolayers were overlaid with 3 ml 1.2% agar (Sigma Chemical Company, St. Louis, MO) and incubated at 37°C under 5% CO₂. When plaques were visible (after two to three days) the overlay was removed, monolayers were stained with 1.2% crystal violet, and plaque forming units were counted.

Results

As shown in **Figure 12A** and **12B**, treatment with the site 195 (RPI 13919) anti-HCV hammerhead enzymatic nucleic acid alone (0 U/ml IFN) resulted in viral replication that was dramatically reduced compared to SAC-treated cells (85%, $P < 0.01$). For both IFN α 2a (**Figure 12A**) or IFN α 2b (**Figure 12B**), treatment with 25 U/ml resulted in a ~90% inhibition of HCV-PV replication in SAC-treated cells as compared to cells treated with SAC alone ($p < 0.01$ for both observations). The maximal level of inhibition in SAC-treated cells (94%) was achieved by treatment with ≥ 50 U/ml of either IFN α 2a or IFN α 2b ($p < 0.01$ for both observations *versus* SAC alone). Maximal inhibition could however, be achieved by a 5-fold lower dose of IFN α 2a (10 U/ml) if enzymatic nucleic acid targeting site 195 in the 5' UTR of HCV RNA was given in combination (**Figure 12A**, $p < 0.01$). While the additional effect of enzymatic nucleic acid treatment on IFN α 2b-treated cells at 10 U/ml was very slight, the combined effect with 25 U/ml IFN α 2b was greater in magnitude (**Figure 12B**). For both interferons tested, pretreatment with 25 U/ml in combination with 200 nM site 195 anti-HCV enzymatic nucleic acid resulted in an even greater level of inhibition of viral replication (>98%) compared to replication in cells treated with 200 nM SAC alone ($P < 0.01$).

A dose response of the site 195 anti-HCV enzymatic nucleic acid was also performed in HeLa cells, either with or without 12.5 U/ml IFN α 2a or IFN α 2b pretreatment. As shown in **Figure 13**, enzymatic nucleic acid-mediated inhibition was dose-dependent and a

significant inhibition of HCV-PV replication ($>75\%$ *versus* 0 nM enzymatic nucleic acid, $P<0.01$) could be achieved by treatment with ≥ 150 nM anti-HCV enzymatic nucleic acid alone (no IFN). However, in IFN-pretreated cells, the dose of anti-HCV enzymatic nucleic acid needed to achieve this level of inhibition was decreased 3-fold to 50 nM ($P<0.01$ *versus* 0 nM enzymatic nucleic acid). In comparison, treatment with the site 195 anti-HCV enzymatic nucleic acid alone at 50 nM resulted in only $\sim 40\%$ inhibition of virus replication. Pretreatment with IFN enhanced the antiviral effect of site 195 enzymatic nucleic acid at all enzymatic nucleic acid doses, compared to no IFN pretreatment.

Interferon- α 1, consensus IFN (CIFN), is another type 1 IFN that is used to treat chronic HCV. To determine if a similar enhancement can occur in CIFN-treated cells, a dose response with CIFN was performed in HeLa cells using 0 U/ml to 12.5 U/ml CIFN in combination with 200 nM site 195 anti-HCV enzymatic nucleic acid or SAC treatment (**Figure 14A**). Again, in the presence of the site 195 anti-HCV enzymatic nucleic acid alone, viral replication was dramatically reduced compared to SAC-treated cells. As shown in **Figure 14A**, treatment with 200 nM anti-HCV enzymatic nucleic acid alone significantly inhibited HCV-PV replication (90% *versus* SAC treatment, $P<0.01$). However, pretreatment with concentrations of CIFN from 1 U/ml to 12.5 U/ml in combination with 200 nM anti-HCV enzymatic nucleic acid resulted in even greater inhibition of viral replication ($>98\%$) compared to replication in cells treated with 200 nM SAC alone ($P<0.01$). It is important to note that pretreatment with 1 U/ml CIFN in SAC-treated cells did not have a significant effect on HCV-poliovirus replication, but in the presence of enzymatic nucleic acid a significant inhibition of replication was observed ($>98\%$, $P<0.01$). Thus, the dose of CIFN needed to achieve a $>98\%$ inhibition could be lowered to 1 U/ml in cells also treated with 200 nM site 195 anti-HCV enzymatic nucleic acid.

A dose response of site 195 anti-HCV enzymatic nucleic acid was then performed in HeLa cells, either with or without 12.5 U/ml CIFN pretreatment. As shown in **Figure 14B**, a significant inhibition of HCV-PV replication ($>95\%$ *versus* 0 nM enzymatic nucleic acid, $P<0.01$) could be achieved by treatment with ≥ 150 nM anti-HCV enzymatic nucleic acid alone. However, in CIFN-pretreated cells, the dose of anti-HCV enzymatic nucleic acid needed to achieve this level of inhibition was only 50 nM ($P<0.01$). In comparison, treatment with the site 195 anti-HCV enzymatic nucleic acid alone at 50 nM resulted in $\sim 50\%$ inhibition

of virus replication. Thus, as was seen with IFN alfa 2a and IFN alfa 2b, the dose of enzymatic nucleic acid could be reduced 3-fold in the presence of CIFN pretreatment to achieve a similar antiviral effect as enzymatic nucleic acid-treatment alone.

To further explore the combination of lower enzymatic nucleic acid concentration and CIFN, a dose response with 0 U/ml to 12.5 U/ml CIFN was subsequently performed in HeLa cells in combination with 50 nM site 195 anti-HCV enzymatic nucleic acid treatment. In multiple experiments, treatment with 50 nM anti-HCV enzymatic nucleic acid alone inhibited HCV-PV replication 50% – 81% compared to viral replication in SAC-treated cells. As for the experiment shown in **Figure 14A**, treatment with CIFN alone at 5 U/ml resulted in ~50% inhibition of viral replication. However, a four hour pretreatment with 5 U/ml CIFN followed by 50 nM anti-HCV enzymatic nucleic acid treatment resulted in 95% - 97% inhibition compared to SAC-treated cells ($P < 0.01$).

To demonstrate that the enhanced antiviral effect of CIFN and enzymatic nucleic acid combination treatment was dependent upon enzymatic nucleic acid cleavage activity, the effect of CIFN in combination with site 195 anti-HCV enzymatic nucleic acid versus the effect of CIFN in combination with a binding competent, attenuated core, control (BAC) was then compared. The BAC can still bind to its specific RNA target, but is greatly diminished in cleavage activity. Pretreatment with 12.5 U/ml CIFN reduced the viral yield ~90% (7-fold) in cells treated with BAC (compare CIFN versus BAC in **Figure 15**). Cells treated with 200 nM site 195 anti-HCV enzymatic nucleic acid alone produced ~95% (17-fold) less virus than BAC-treated cells (195 RZ BAC in **Figure 15**). The combination of CIFN pretreatment and 200 nM site 195 anti-HCV enzymatic nucleic acid results in an augmented >98% (300-fold) reduction in viral yield (CIFN+RZ versus control in **Figure 15**).

Cell Culture Assays

Although there have been reports of replication of HCV in cell culture (see below), these systems are difficult to replicate and have proven unreliable. Therefore, as was the case for development of other anti-HCV therapeutics such as interferon and ribavirin, after demonstration of safety in animal studies applicant can proceed directly into a clinical feasibility study.

Several recent reports have documented *in vitro* growth of HCV in human cell lines (Mizutani *et al.*, Biochem Biophys Res Commun 1996 227(3):822-826; Tagawa *et al.*, Journal of Gastroenterology and Hepatology 1995 10(5):523-527; Cribier *et al.*, Journal of General Virology 76(10):2485-2491; Seipp *et al.*, Journal of General Virology 1997 78(10):2467-2478; Iacovacci *et al.*, Research Virology 1997 148(2):147-151; Iacovacci *et al.*, Hepatology 1997 26(5):1328-1337; Ito *et al.*, Journal of General Virology 1996 77(5):1043-1054; Nakajima *et al.*, Journal of Virology 1996 70(5):3325-3329; Mizutani *et al.*, Journal of Virology 1996 70(10):7219-7223; Valli *et al.*, Res Virol 1995 146(4):285-288; Kato *et al.*, Biochem Biophys Res Comm 1995 206(3):863-869). Replication of HCV has been demonstrated in both T and B cell lines as well as cell lines derived from human hepatocytes. Demonstration of replication was documented using either RT-PCR based assays or the b-DNA assay. It is important to note that the most recent publications regarding HCV cell cultures document replication for up to 6-months.

Additionally, another recent study has identified more robust strains of hepatitis C virus having adaptive mutations that allow the strains to replicate more vigorously in human cell culture (Rockefeller University, www.sciencedaily.com/releases/2000/12/001211075228.htm). The mutations that confer this enhanced ability to replicate are located in a specific region of a protein identified as NS5A. Studies performed at Rockefeller University have shown that in certain cell culture systems, infection with the robust strains produces a 10,000-fold increase in the number of infected cells. The greatly increased availability of HCV-infected cells in culture can be used to develop high-throughput screening assays, in which a large number of compounds, such as enzymatic nucleic acid molecules, can be tested to determine their effectiveness.

In addition to cell lines that can be infected with HCV, several groups have reported the successful transformation of cell lines with cDNA clones of full-length or partial HCV genomes (Harada *et al.*, Journal of General Virology 1995 76(5):1215-1221; Haramatsu *et al.*, Journal of Viral Hepatitis 1997 4S(1):61-67; Dash *et al.*, American Journal of Pathology 1997 151(2):363-373; Mizuno *et al.*, Gastroenterology 1995 109(6):1933-40; Yoo *et al.*, Journal of Virology 1995 69(1):32-38).

Animal Models

The best characterized animal system for HCV infection is the chimpanzee. Moreover, the chronic hepatitis that results from HCV infection in chimpanzees and humans is very similar. Although clinically relevant, the chimpanzee model suffers from several practical impediments that make use of this model difficult. These include; high cost, long incubation requirements and lack of sufficient quantities of animals. Due to these factors, a number of groups have attempted to develop rodent models of chronic hepatitis C infection. While direct infection has not been possible several groups have reported on the stable transfection of either portions or entire HCV genomes into rodents (Yamamoto *et al.*, Hepatology 1995 22(3): 847-855; Galun *et al.*, Journal of Infectious Disease 1995 172(1):25-30; Koike *et al.*, Journal of general Virology 1995 76(12):3031-3038; Pasquinelli *et al.*, Hepatology 1997 25(3): 719-727; Hayashi *et al.*, Princess Takamatsu Symp 1995 25:1430149; Mariya K, Yotsuyanagi H, Shintani Y, Fujie H, Ishibashi K, Matsuura Y, Miyamura T, Koike K. Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. Journal of General Virology 1997 78(7) 1527-1531; Takehara *et al.*, Hepatology 1995 21(3):746-751; Kawamura *et al.*, Hepatology 1997 25(4): 1014-1021). In addition, transplantation of HCV infected human liver into immunocompromised mice results in prolonged detection of HCV RNA in the animal's blood.

Vierling, International PCT Publication No. WO 99/16307, describes a method for expressing hepatitis C virus in an *in vivo* animal model. Viable, HCV infected human hepatocytes are transplanted into a liver parenchyma of a scid/scid mouse host. The scid/scid mouse host is then maintained in a viable state, whereby viable, morphologically intact human hepatocytes persist in the donor tissue and hepatitis C virus is replicated in the persisting human hepatocytes. This model provides an effective means for the study of HCV inhibition by enzymatic nucleic acids *in vivo*.

Diagnostic uses

Enzymatic nucleic acids of this invention may be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of *HCV* RNA in a cell. The close relationship between enzymatic nucleic acid activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple enzymatic nucleic acids described in this invention, one may map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of

target RNAs with enzymatic nucleic acids may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple enzymatic nucleic acids targeted to different genes, enzymatic nucleic acids coupled with known small molecule inhibitors, or intermittent treatment with combinations of enzymatic nucleic acids and/or other chemical or biological molecules). Other *in vitro* uses of enzymatic nucleic acids of this invention are well known in the art, and include detection of the presence of mRNAs associated with HCV related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a enzymatic nucleic acid using standard methodology.

In a specific example, enzymatic nucleic acids which can cleave only wild-type or mutant forms of the target RNA are used for the assay. The first enzymatic nucleic acid is used to identify wild-type RNA present in the sample and the second enzymatic nucleic acid will be used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA will be cleaved by both enzymatic nucleic acids to demonstrate the relative enzymatic nucleic acid efficiencies in the reactions and the absence of cleavage of the “non-targeted” RNA species. The cleavage products from the synthetic substrates will also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus each analysis will require two enzymatic nucleic acids, two substrates and one unknown sample which will be combined into six reactions. The presence of cleavage products will be determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, HCV) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios will be correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

Additional Uses

Potential usefulness of sequence-specific enzymatic nucleic acid molecules of the instant invention might have many of the same applications for the study of RNA that DNA restriction endonucleases have for the study of DNA (Nathans *et al.*, 1975 *Ann. Rev. Biochem.* 44:273). For example, the pattern of restriction fragments could be used to establish sequence relationships between two related RNAs, and large RNAs could be specifically cleaved to fragments of a size more useful for study. The ability to engineer sequence specificity of the enzymatic nucleic acid molecule is ideal for cleavage of RNAs of unknown sequence. Applicant describes the use of nucleic acid molecules to down-regulate gene expression of target genes in bacterial, microbial, fungal, viral, and eukaryotic systems including plant, or mammalian cells.

TABLE I

Characteristics of naturally occurring ribozymes

Group I Introns

- 5
 - Size: ~150 to >1000 nucleotides.
 - Requires a U in the target sequence immediately 5' of the cleavage site.
 - Binds 4-6 nucleotides at the 5'-side of the cleavage site.
 - Reaction mechanism: attack by the 3'-OH of guanosine to generate cleavage products with 3'-OH and 5'-guanosine.
- 10
 - Additional protein cofactors required in some cases to help folding and maintenance of the active structure.
 - Over 300 known members of this class. Found as an intervening sequence in *Tetrahymena thermophila* rRNA, fungal mitochondria, chloroplasts, phage T4, blue-green algae, and others.
- 15
 - Major structural features largely established through phylogenetic comparisons, mutagenesis, and biochemical studies [ⁱ, ⁱⁱ].
 - Complete kinetic framework established for one ribozyme [ⁱⁱⁱ, ^{iv}, ^v, ^{vi}].
 - Studies of ribozyme folding and substrate docking underway [^{vii}, ^{viii}, ^{ix}].
 - Chemical modification investigation of important residues well established [^x, ^{xi}].
- 20
 - The small (4-6 nt) binding site may make this ribozyme too non-specific for targeted RNA cleavage, however, the *Tetrahymena* group I intron has been used to repair a "defective" β -galactosidase message by the ligation of new β -galactosidase sequences onto the defective message [^{xii}].

25 RNase P RNA (M1 RNA)

- Size: ~290 to 400 nucleotides.
- RNA portion of a ubiquitous ribonucleoprotein enzyme.
- Cleaves tRNA precursors to form mature tRNA [^{xiii}].

- Reaction mechanism: possible attack by M^{2+} -OH to generate cleavage products with 3'-OH and 5'-phosphate.
 - RNase P is found throughout the prokaryotes and eukaryotes. The RNA subunit has been sequenced from bacteria, yeast, rodents, and primates.
- 5
- Recruitment of endogenous RNase P for therapeutic applications is possible through hybridization of an External Guide Sequence (EGS) to the target RNA [xiv, xv]
 - Important phosphate and 2' OH contacts recently identified [xvi, xvii]

Group II Introns

- 10
- Size: >1000 nucleotides.
 - Trans cleavage of target RNAs recently demonstrated [xviii, xix].
 - Sequence requirements not fully determined.
- 15
- Reaction mechanism: 2'-OH of an internal adenosine generates cleavage products with 3'-OH and a "lariat" RNA containing a 3'-5' and a 2'-5' branch point.
 - Only natural ribozyme with demonstrated participation in DNA cleavage [xx, xxi] in addition to RNA cleavage and ligation.
 - Major structural features largely established through phylogenetic comparisons [xxii].
 - Important 2' OH contacts beginning to be identified [xxiii]
- 20
- Kinetic framework under development [xxiv]

Neurospora VS RNA

- Size: ~144 nucleotides.
- 25
- Trans cleavage of hairpin target RNAs recently demonstrated [xxv].
 - Sequence requirements not fully determined.
 - Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
 - Binding sites and structural requirements not fully determined.
- 30
- Only 1 known member of this class. Found in Neurospora VS RNA.

Hammerhead Ribozyme

(see text for references)

- Size: ~13 to 40 nucleotides.
- 5 • Requires the target sequence UH immediately 5' of the cleavage site.
- Binds a variable number nucleotides on both sides of the cleavage site.
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- 10 • 14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious agent.
- Essential structural features largely defined, including 2 crystal structures [^{xxvi}, ^{xxvii}]
- Minimal ligation activity demonstrated (for engineering through *in vitro* selection) [^{xxviii}]
- Complete kinetic framework established for two or more ribozymes [^{xxix}].
- Chemical modification investigation of important residues well established [^{xxx}].

Hairpin Ribozyme

- Size: ~50 nucleotides.
- Requires the target sequence GUC immediately 3' of the cleavage site.
- 20 • Binds 4-6 nucleotides at the 5'-side of the cleavage site and a variable number to the 3'-side of the cleavage site.
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- 25 • 3 known members of this class. Found in three plant pathogen (satellite RNAs of the tobacco ringspot virus, arabis mosaic virus and chicory yellow mottle virus) which uses RNA as the infectious agent.
- Essential structural features largely defined [^{xxxi}, ^{xxxii}, ^{xxxiii}, ^{xxxiv}]
- Ligation activity (in addition to cleavage activity) makes ribozyme amenable to engineering through *in vitro* selection [^{xxxv}]
- 30 • Complete kinetic framework established for one ribozyme [^{xxxvi}].
- Chemical modification investigation of important residues begun [^{xxxvii}, ^{xxxviii}].

Hepatitis Delta Virus (HDV) Ribozyme

- Size: ~60 nucleotides.
- 5 • Trans cleavage of target RNAs demonstrated [^{xxxix}].
- Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required. Folded ribozyme contains a pseudoknot structure [^{xi}].
- Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
- 10 • Only 2 known members of this class. Found in human HDV.
- Circular form of HDV is active and shows increased nuclease stability [^{xli}]

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Table II:

A. 2.5 μ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* RNA
Phosphoramidites	6.5	163 μ L	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 μ L	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 μ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 μ L	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 μ L	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 μ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* RNA
Phosphoramidites	15	31 μ L	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 μ L	45 sec	233 min	465 sec
Acetic Anhydride	655	124 μ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 μ L	5 sec	5 sec	5 sec
TCA	700	732 μ L	10 sec	10 sec	10 sec
Iodine	20.6	244 μ L	15 sec	15 sec	15 sec
Beaucage	7.7	232 μ L	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 μ mol Synthesis Cycle 96 well Instrument

Reagent	Equivalents	Amount	Wait Time		
			DNA/2'-O-methyl/Ribo	* DNA	* 2'-O-methyl
Phosphoramidites	22/33/66	40/60/120 μ L		60 sec	180 sec
S-Ethyl Tetrazole	70/105/210	40/60/120 μ L		60 sec	180 min
Acetic Anhydride	265/265/265	50/50/50 μ L		10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 μ L		10 sec	10 sec
TCA	238/475/475	250/500/500 μ L		15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 μ L		30 sec	30 sec
Beaucage	34/51/51	80/120/120		100 sec	200 sec
Acetonitrile	NA	1150/1150/1150 μ L		NA	NA

- Wait time does not include contact time during delivery.

Table III: HCV DNzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNzyme	Seq ID
10	UGGGGGCG A CACUCCAC	1	GTGGAGTG GGCTAGCTACAACGA CGCCCCCA	4798
12	GGGGCGAC A CUCCACCA	2	TGGTGGAG GGCTAGCTACAACGA GTCGCCCC	4799
17	GACACUCC A CCAUAGAU	3	ATCTATGG GGCTAGCTACAACGA GGAGTGTC	4800
20	ACUCCACC A UAGAUCAC	4	GTGATCTA GGCTAGCTACAACGA GGTGGAGT	4801
24	CACCAUAG A UCACUCCC	5	GGGAGTGA GGCTAGCTACAACGA CTATGGTG	4802
27	CAUAGAUC A CUCCCCUG	6	CAGGGGAG GGCTAGCTACAACGA GATCTATG	4803
35	ACUCCCCU G UGAGGAAC	7	GTTCTCTA GGCTAGCTACAACGA AGGGGAGT	4804
42	UGUGAGGA A CUACUGUC	8	GACAGTAG GGCTAGCTACAACGA TCCTCACA	4805
45	GAGGAACU A CUGUCUUC	9	GAAGACAG GGCTAGCTACAACGA AGTTCCTC	4806
48	GAACUACU G UCUUACG	10	CGTGAAGG GGCTAGCTACAACGA AGTAGTTC	4807
54	CUGUCUUC A CGCAGAAA	11	TTTCTGCG GGCTAGCTACAACGA GAAGACAG	4808
56	GUCUUCAC G CAGAAAGC	12	GCTTTCTG GGCTAGCTACAACGA GTGAAGAC	4809
63	CGCAGAAA G CGUCUAGC	13	GCTAGACG GGCTAGCTACAACGA TTTCTGCG	4810
65	CAGAAAGC G UCUAGCCA	14	TGGCTAGA GGCTAGCTACAACGA GCTTTCTG	4811
70	AGCGUCUA G CCAUGGCG	15	CGCCATGG GGCTAGCTACAACGA TAGACGCT	4812
73	GUCUAGCC A UGGCGUUA	16	TAACGCCA GGCTAGCTACAACGA GGCTAGAC	4813
76	UAGCCAUG G CGUUAUGA	17	TACTAACG GGCTAGCTACAACGA CATGGCTA	4814
78	GCCAUGGC G UUAGUAUG	18	CATACTAA GGCTAGCTACAACGA GCCATGGC	4815
82	UGGCGUUA G UAUGAGUG	19	CACTCATA GGCTAGCTACAACGA TAACGCCA	4816
84	GCGUUAUG A UGAGUGUC	20	GACACTCA GGCTAGCTACAACGA ACTAACGC	4817
88	UAGUAUGA G UGUCGUGC	21	GCACGACA GGCTAGCTACAACGA TCATACTA	4818
90	GUAUGAGU G UCGUGCAG	22	CTGCACGA GGCTAGCTACAACGA ACTCATAC	4819
93	UGAGUGUC G UGCAGCCU	23	AGGCTGCA GGCTAGCTACAACGA GACACTCA	4820
95	AGUGUCGU G CAGCCUCC	24	GGAGGCTG GGCTAGCTACAACGA ACGACACT	4821
98	GUCGUGCA G CCUCCAGG	25	CCTGGAGG GGCTAGCTACAACGA TGCACGAC	4822
107	CCUCCAGG A CCCCCCU	26	AGGGGGGG GGCTAGCTACAACGA CCTGGAGG	4823
125	CCGGGAGA G CCAUAGUG	27	CACTATGG GGCTAGCTACAACGA TCTCCCGG	4824
128	GGAGAGCC A UAGUGGUC	28	GACCACTA GGCTAGCTACAACGA GGCTCTCC	4825
131	GAGCCAU A UGGUCUGC	29	GCAGACCA GGCTAGCTACAACGA TATGGCTC	4826
134	CCAUAUG G UCUGCGGA	30	TCCGCAGA GGCTAGCTACAACGA CACTATGG	4827
138	AGUGGUCU G CGGAACCG	31	CGGTTCGG GGCTAGCTACAACGA AGACCACT	4828
143	UCUGCGGA A CCGGUGAG	32	CTCACCGG GGCTAGCTACAACGA TCCGCAGA	4829
147	CGGAACCG G UGAGUACA	33	TGTACTCA GGCTAGCTACAACGA CGGTTCGG	4830
151	ACCGGUGA G UACACCGG	34	CCGGTGTA GGCTAGCTACAACGA TCACCGGT	4831
153	CGGUGAGU A CACCGGAA	35	TTCCGGTG GGCTAGCTACAACGA ACTCACCG	4832
155	GUGAGUAC A CCGGAAUU	36	AATTCCGG GGCTAGCTACAACGA GTACTCAC	4833
161	ACACCGGA A UUGCCAGG	37	CCTGGCAA GGCTAGCTACAACGA TCCGGTGT	4834
164	CCGGAAUU G CCAGGACG	38	CGTCTTGG GGCTAGCTACAACGA AATTCCGG	4835
170	UUGCCAGG A CGACCGGG	39	CCCGGTCG GGCTAGCTACAACGA CCTGGCAA	4836
173	CCAGGACG A CCGGGUCC	40	GGACCCGG GGCTAGCTACAACGA CGTCTTGG	4837
178	ACGACCGG G UCCUUUCU	41	AGAAAGGA GGCTAGCTACAACGA CCGGTCGT	4838
190	UUUCUUGG A UCAACCCG	42	CGGGTTGA GGCTAGCTACAACGA CCAAGAAA	4839
194	UUGGAUCA A CCCGCUCA	43	TGAGCGGG GGCTAGCTACAACGA TGATCCAA	4840
198	AUCAACCC G CUCAAUGC	44	GCATTGAG GGCTAGCTACAACGA GGGTTGAT	4841
203	CCCGCUCA A UGCCUGGA	45	TCCAGGCA GGCTAGCTACAACGA TGAGCGGG	4842
205	CGCUCAAU G CCUGGAGA	46	TCTCCAGG GGCTAGCTACAACGA ATTGAGCG	4843
213	GCCUGGAG A UUUGGGCG	47	CGCCAAA GGCTAGCTACAACGA CTCCAGGC	4844
219	AGAUUUGG G CGUGCCCC	48	GGGGCAG GGCTAGCTACAACGA CCAAATCT	4845
221	AUUUGGGC G UGCCCCCG	49	CGGGGGCA GGCTAGCTACAACGA GCCCAAAT	4846
223	UUGGGCGU G CCCCCGCG	50	CGCGGGGG GGCTAGCTACAACGA ACGCCCAA	4847
229	GUGCCCCC G CGAGACUG	51	CAGTCTCG GGCTAGCTACAACGA GGGGGCAC	4848
234	CCCGCGAG A CUGCUAGC	52	GCTAGCAG GGCTAGCTACAACGA CTCGCGGG	4849

237	GCGAGACU G CUAGCCGA	53	TCGGCTAG GGCTAGCTACAACGA AGTCTCGC	4850
241	GACUGCUA G CCGAGUAG	54	CTACTCGG GGCTAGCTACAACGA TAGCAGTC	4851
246	CUAGCCGA G UAGUGUUG	55	CAACACTA GGCTAGCTACAACGA TCGGCTAG	4852
249	GCCGAGUA G UGUUGGGU	56	ACCCAACA GGCTAGCTACAACGA TACTCGGC	4853
251	CGAGUAGU G UUGGGUCG	57	CGACCCAA GGCTAGCTACAACGA ACTACTCG	4854
256	AGUGUUGG G UCGCGAAA	58	TTTCGCGA GGCTAGCTACAACGA CCAACACT	4855
259	GUUGGGUC G CGAAAGGC	59	GCCTTTTCG GGCTAGCTACAACGA GACCCAAC	4856
266	CGCGAAAG G CCUUGUGG	60	CCACAAGG GGCTAGCTACAACGA CTTTCGCG	4857
271	AAGGCCUU G UGGUACUG	61	CAGTACCA GGCTAGCTACAACGA AAGGCCTT	4858
274	GCCUUGUG G UACUGCCU	62	AGGCAGTA GGCTAGCTACAACGA CACAAGGC	4859
276	CUUGUGGU A CUGCCUGA	63	TCAGGCAG GGCTAGCTACAACGA ACCACAAG	4860
279	GUGGUACU G CCUGAUAG	64	CTATCAGG GGCTAGCTACAACGA AGTACCAC	4861
284	ACUGCCUG A UAGGGUGC	65	GCACCCTA GGCTAGCTACAACGA CAGGCAGT	4862
289	CUGAUAGG G UGCUUGCG	66	CGCAAGCA GGCTAGCTACAACGA CCTATCAG	4863
291	GAUAGGGU G CUUGCGAG	67	CTCGCAAG GGCTAGCTACAACGA ACCCTATC	4864
295	GGGUGCUU G CGAGUGCC	68	GGCACTCG GGCTAGCTACAACGA AAGCACCC	4865
299	GCUUGCGA G UGCCCCGG	69	CCGGGGCA GGCTAGCTACAACGA TCGCAAGC	4866
301	UUGCGAGU G CCCC GGGA	70	TCCCGGGG GGCTAGCTACAACGA ACTCGCAA	4867
311	CCCGGGAG G UCUCGUAG	71	CTACGAGA GGCTAGCTACAACGA CTCCCGGG	4868
316	GAGGUCUC G UAGACCGU	72	ACGGTCTA GGCTAGCTACAACGA GAGACCTC	4869
320	UCUCGUAG A CCGUGCAC	73	GTGCACGG GGCTAGCTACAACGA CTACGAGA	4870
323	CGUAGACC G UGCACCAU	74	ATGGTGCA GGCTAGCTACAACGA GGTCTACG	4871
325	UAGACCGU G CACCAUGA	75	TCATGGTG GGCTAGCTACAACGA ACGGTCTA	4872
327	GACCGUGC A CCAUGAGC	76	GCTCATGG GGCTAGCTACAACGA GCACGGTC	4873
330	CGUGCACC A UGAGCAG	77	CGTGCTCA GGCTAGCTACAACGA GGTGCACG	4874
334	CACCAUGA G CACGAAUC	78	GATTTCGTG GGCTAGCTACAACGA TCATGGTG	4875
336	CCAUGAGC A CGAAUCCU	79	AGGATTTCG GGCTAGCTACAACGA GCTCATGG	4876
340	GAGCACGA A UCCUAAAC	80	GTTTAGGA GGCTAGCTACAACGA TCGTGCTC	4877
347	AAUCCUAA A CCUCAAAG	81	CTTTGAGG GGCTAGCTACAACGA TTAGGATT	4878
360	AAAGAAAA A CCAAACGU	82	ACGTTTGG GGCTAGCTACAACGA TTTTCTTT	4879
365	AAAACCAA A CGUAAAC	83	GTGTTACG GGCTAGCTACAACGA TTGGTTTT	4880
367	AACCAAAC G UAACACCA	84	TGGTGTTA GGCTAGCTACAACGA GTTTGGTT	4881
370	CAAACGUA A CACCAACC	85	GCTTGGTG GGCTAGCTACAACGA TACGTTTG	4882
372	AACGUAAC A CCAACCGC	86	GCGTTTGG GGCTAGCTACAACGA GTTACGTT	4883
376	UAACACCA A CCGCCGCC	87	GGCGGCGG GGCTAGCTACAACGA TGGTGTTA	4884
379	CACCAACC G CCGCCAC	88	GTGGGCGG GGCTAGCTACAACGA GGTGGTG	4885
382	CAACCGCC G CCCACAGG	89	CCTGTGGG GGCTAGCTACAACGA GGCGGTTG	4886
386	CGCCGCC A CAGGACGU	90	ACGTCCTG GGCTAGCTACAACGA GGGCGGCG	4887
391	CCCACAGG A CGUCAAGU	91	ACTTGACG GGCTAGCTACAACGA CCTGTGGG	4888
393	CACAGGAC G UCAAGUUC	92	GAAC TTGA GGCTAGCTACAACGA GTCCTGTG	4889
398	GACGUCAA G UUCCCGGG	93	CCCGGGAA GGCTAGCTACAACGA TTGACGTC	4890
406	GUUCCCGG G CGGUGGUC	94	GACCACCG GGCTAGCTACAACGA CCGGGAAC	4891
409	CCCGGGCG G UGGUCAGA	95	TCTGACCA GGCTAGCTACAACGA CGCCCGGG	4892
412	GGGCGGUG G UCAGAUCC	96	CGATCTGA GGCTAGCTACAACGA CACCGCCC	4893
417	GUGGUCAG A UCGUUGGU	97	ACCAACGA GGCTAGCTACAACGA CTGACCAC	4894
420	GUCAGAUCC G UUGGUGGA	98	TCCACCAA GGCTAGCTACAACGA GATCTGAC	4895
424	GAUCGUUG G UGGAGUUU	99	AAACTCCA GGCTAGCTACAACGA CAACGATC	4896
429	UUGGUGGA G UUUACCUG	100	CAGGTAAA GGCTAGCTACAACGA TCCACCAA	4897
433	UGGAGUUU A CCUGUUGC	101	GCAACAGG GGCTAGCTACAACGA AAAC TCCA	4898
437	GUUUACCU G UUGCCGCG	102	CGCGGCAA GGCTAGCTACAACGA AGGTAAAC	4899
440	UACCUGUU G CCGCGCAG	103	CTGCGCGG GGCTAGCTACAACGA AACAGGTA	4900
443	CUGUUGCC G CGCAGGGG	104	CCCCTGCG GGCTAGCTACAACGA GGCAACAG	4901
445	GUUGCCGC G CAGGGGCC	105	GGCCCTTG GGCTAGCTACAACGA GCGGCAAC	4902
451	GCGCAGGG G CCCAGGU	106	ACCTGGGG GGCTAGCTACAACGA CCCTGCGC	4903
458	GGCCCCAG G UUGGUGU	107	ACACCCAA GGCTAGCTACAACGA CTGGGGCC	4904
463	CAGGUUGG G UUGCGCG	108	CGCGCACA GGCTAGCTACAACGA CCAACCTG	4905
465	GGUUGGGU G UGCGCGCG	109	CGCGCGCA GGCTAGCTACAACGA ACCCAACC	4906

467	UUGGGUGU G CGCGCGAC	110	GTCGCGCG GGCTAGCTACAACGA ACACCCAA	4907
469	GGGUGUGC G CGCGACUA	111	TAGTCGCG GGCTAGCTACAACGA GCACACCC	4908
471	GUGUGCGC G CGACUAGG	112	CCTAGTCG GGCTAGCTACAACGA GCGCACAC	4909
474	UGCGCGCG A CUAGGAAG	113	CTTCCTAG GGCTAGCTACAACGA CGCGCGCA	4910
483	CUAGGAAG A CUUCCGAG	114	CTCGGAAG GGCTAGCTACAACGA CTTCCTAG	4911
491	ACUUCCGA G CGGUCGCA	115	TGCGACCG GGCTAGCTACAACGA TCGGAAGT	4912
494	UCCGAGCG G UCGCAACC	116	GGTTGCGA GGCTAGCTACAACGA CGCTCGGA	4913
497	GAGCGGUC G CAACCUCG	117	CGAGGTTG GGCTAGCTACAACGA GACCGCTC	4914
500	CGGUCGCA A CCUCGUGG	118	CCACGAGG GGCTAGCTACAACGA TGCGACCG	4915
505	GCAACCUC G UGGAAGGC	119	GCCTTCCA GGCTAGCTACAACGA GAGGTTGC	4916
512	CGUGGAAG G CGACAACC	120	GGTTGTCG GGCTAGCTACAACGA CTTCACG	4917
515	GGAAGGCG A CAACCUAU	121	ATAGGTTG GGCTAGCTACAACGA CGCCTTCC	4918
518	AGGCGACA A CCUAUCCC	122	GGGATAGG GGCTAGCTACAACGA TGTCGCCT	4919
522	GACAACCU A UCCCCAAG	123	CTTGGGGA GGCTAGCTACAACGA AGGTTGTC	4920
531	UCCCCAAG G CUCGCCGG	124	CCGCGCAG GGCTAGCTACAACGA CTTGGGGA	4921
535	CAAGGCUC G CCGGCCCG	125	CGGGCCGG GGCTAGCTACAACGA GAGCCTTG	4922
539	GCUCGCCG G CCCGAGGG	126	CCCTCGGG GGCTAGCTACAACGA CGGCGAGC	4923
547	GCCCCAGG G CAGGGCCU	127	AGGCCCTG GGCTAGCTACAACGA CCTCGGGC	4924
552	AGGGCAGG G CCUGGGCU	128	AGCCCAGG GGCTAGCTACAACGA CCTGCCCT	4925
558	GGGCCUGG G CUCAGCCC	129	GGGCTGAG GGCTAGCTACAACGA CCAGGCC	4926
563	UGGGCUCA G CCCGGGUA	130	TACCCGGG GGCTAGCTACAACGA TGAGCCCA	4927
569	CAGCCCGG G UACCCUUG	131	CAAGGGTA GGCTAGCTACAACGA CCGGGCTG	4928
571	GCCCCGGU A CCCUUGGC	132	GCCAAGGG GGCTAGCTACAACGA ACCCGGGC	4929
578	UACCCUUG G CCCCUUA	133	TAGAGGGG GGCTAGCTACAACGA CAAGGGTA	4930
586	GCCCCUCU A UGGCAAUG	134	CATTGCCA GGCTAGCTACAACGA AGAGGGGC	4931
589	CCUCUAUG G CAAUGAGG	135	CCTCATTG GGCTAGCTACAACGA CATAGAGG	4932
592	CUAUGGCA A UGAGGGCU	136	AGCCCTCA GGCTAGCTACAACGA TGCCATAG	4933
598	CAAUGAGG G CUUAGGGU	137	ACCCTAAG GGCTAGCTACAACGA CCTCATTG	4934
605	GGCUUAGG G UGGGCAGG	138	CCTGCCCA GGCTAGCTACAACGA CCTAAGCC	4935
609	UAGGGUGG G CAGGAUGG	139	CCATCCTG GGCTAGCTACAACGA CCACCCTA	4936
614	UGGGCAGG A UGGCUCCU	140	AGGAGCCA GGCTAGCTACAACGA CCTGCCCA	4937
617	GCAGGAUG G CUCCUGUC	141	GACAGGAG GGCTAGCTACAACGA CATCCTGC	4938
623	UGGCUCCU G UCACCCCG	142	CGGGGTGA GGCTAGCTACAACGA AGGAGCCA	4939
626	CUCCUGUC A CCCC GCCG	143	CCGGGGGG GGCTAGCTACAACGA GACAGGAG	4940
631	GUCACCCC G CGGCUCCC	144	GGGAGCCG GGCTAGCTACAACGA GGGGTGAC	4941
634	ACCCCGCG G CUCCCGGC	145	GCCGGGAG GGCTAGCTACAACGA CGCGGGGT	4942
641	GGCUCCCG G CCUAGUUG	146	CAACTAGG GGCTAGCTACAACGA CGGGAGCC	4943
646	CCGGCCUA G UUGGGGCC	147	GGCCCCAA GGCTAGCTACAACGA TAGGCCGG	4944
652	UAGUUGGG G CCCCACGG	148	CCGTGGGG GGCTAGCTACAACGA CCCAATA	4945
657	GGGGCCCC A CGGACCCC	149	GGGGTCCG GGCTAGCTACAACGA GGGGCCCC	4946
661	CCCCACGG A CCCC CGC	150	GCCGGGGG GGCTAGCTACAACGA CCGTGGGG	4947
668	GACCCCGG G CGUAGGUC	151	GACCTACG GGCTAGCTACAACGA CGGGGGTC	4948
670	CCCCCGGC G UAGGUCGC	152	GCGACCTA GGCTAGCTACAACGA GCCGGGGG	4949
674	CGGCGUAG G UCGCGUAA	153	TTACGCGA GGCTAGCTACAACGA CTACGCCG	4950
677	CGUAGGUC G CGUAAUU	154	AAGTTACG GGCTAGCTACAACGA GACCTACG	4951
679	UAGGUCGC G UAACUUGG	155	CCAAGTTA GGCTAGCTACAACGA GCGACCTA	4952
682	GUCGCGUA A CUUGGGUA	156	TACCCAAG GGCTAGCTACAACGA TACGCGAC	4953
688	UAACUUGG G UAAGGUCA	157	TGACCTTA GGCTAGCTACAACGA CCAAGTTA	4954
693	UGGGUAAG G UCAUCGAU	158	ATCGATGA GGCTAGCTACAACGA CTACCCA	4955
696	GUAAGGUC A UCGAUACC	159	GGTATCGA GGCTAGCTACAACGA GACCTTAC	4956
700	GGUCAUCG A UACCCUCA	160	TGAGGGTA GGCTAGCTACAACGA CGATGACC	4957
702	UCAUCGAU A CCCUCACA	161	TGTGAGGG GGCTAGCTACAACGA ATCGATGA	4958
708	AUACCCUC A CAUGCGGC	162	GCCGCATG GGCTAGCTACAACGA GAGGGTAT	4959
710	ACCCUCAC A UGCGGCUU	163	AAGCCGCA GGCTAGCTACAACGA GTGAGGGT	4960
712	CCUCACAU G CGGCUUCG	164	CGAAGCCG GGCTAGCTACAACGA ATGTGAGG	4961
715	CACAUGCG G CUUCGCCG	165	CGGCGAAG GGCTAGCTACAACGA CGCATGTG	4962
720	GCGGCUUC G CCGACCUC	166	GAGGTCGG GGCTAGCTACAACGA GAAGCCGC	4963

724	CUUCGCCG A CCUCAUGG	167	CCATGAGG GGCTAGCTACAACGA CGGCGAAG	4964
729	CCGACCUC A UGGGGUAC	168	GTACCCCA GGCTAGCTACAACGA GAGGTCGG	4965
734	CUCAUGGG G UACAUUCC	169	GGAATGTA GGCTAGCTACAACGA CCCATGAG	4966
736	CAUGGGGU A CAUUCGCG	170	GCGGAATG GGCTAGCTACAACGA ACCCCATG	4967
738	UGGGGUAC A UUCGCGUC	171	GAGCGGAA GGCTAGCTACAACGA GTACCCCA	4968
743	UACAUUCC G CUCGUCGG	172	CCGACGAG GGCTAGCTACAACGA GGAATGTA	4969
747	UUCGCGUC G UCGGCGCC	173	GGCGCCGA GGCTAGCTACAACGA GAGCGGAA	4970
751	GCUCGUCG G CGCCCCU	174	AGGGGGCG GGCTAGCTACAACGA CGACGAGC	4971
753	UCGUCGGC G CCCCCUUG	175	CAAGGGGG GGCTAGCTACAACGA GCCGACGA	4972
766	CUUGGGAG G CACUGCCA	176	TGGCAGTG GGCTAGCTACAACGA CTCCCAAG	4973
768	UGGGAGGC A CUGCCAGG	177	CCTGGCAG GGCTAGCTACAACGA GCCTCCCA	4974
771	GAGGCACU G CCAGGGCC	178	GGCCCTGG GGCTAGCTACAACGA AGTGCCTC	4975
777	CUGCCAGG G CCCUGGCG	179	CGCCAGGG GGCTAGCTACAACGA CCTGGCAG	4976
783	GGGCCCUG G CGCAUGGC	180	GCCATGCG GGCTAGCTACAACGA CAGGGCCC	4977
785	GCCCUGGC G CAUGGCGU	181	ACGCCATG GGCTAGCTACAACGA GCCAGGGC	4978
787	CCUGGCGC A UGGCGUCC	182	GGACGCCA GGCTAGCTACAACGA GCGCCAGG	4979
790	GGCGCAUG G CGUCCGGG	183	CCCGGACG GGCTAGCTACAACGA CATGCGCC	4980
792	CGCAUGGC G UCCGGGUU	184	AACCCGGA GGCTAGCTACAACGA GCCATGCG	4981
798	GCGUCCGG G UUCUGGAA	185	TTCCAGAA GGCTAGCTACAACGA CCGGACGC	4982
808	UCUGGAAG A CGGCGUGA	186	TCACGCCG GGCTAGCTACAACGA CTTCCAGA	4983
811	GGAAGACG G CGUGAACU	187	AGTTCACG GGCTAGCTACAACGA CGTCTTCC	4984
813	AAGACGGC G UGAACUAA	188	ATAGTTCA GGCTAGCTACAACGA GCGTCTTT	4985
817	CGGCGUGA A CUAUGCAA	189	TTGCATAG GGCTAGCTACAACGA TCACGCCG	4986
820	CGUGAACU A UGCAACAG	190	CTGTTGCA GGCTAGCTACAACGA AGTTCACG	4987
822	UGAACUAA G CAACAGGG	191	CCCTGTTG GGCTAGCTACAACGA ATAGTTCA	4988
825	ACUAUGCA A CAGGGAAU	192	ATTCCCTG GGCTAGCTACAACGA TGCATAGT	4989
832	AACAGGGA A UCUGCCCG	193	CGGGCAGA GGCTAGCTACAACGA TCCCTGTT	4990
836	GGGAAUCU G CCCGGUUG	194	CAACCGGG GGCTAGCTACAACGA AGATTCCC	4991
841	UCUGCCCG G UUGCUCUU	195	AAGAGCAA GGCTAGCTACAACGA CGGGCAGA	4992
844	GCCCGGUU G CUCUUUCU	196	AGAAAGAG GGCTAGCTACAACGA AACCAGGC	4993
855	CUUUCUCU A UCUUCCUC	197	GAGGAAGA GGCTAGCTACAACGA AGAGAAAG	4994
867	UCCUCUUG G CUCUGCUG	198	CAGCAGAG GGCTAGCTACAACGA CAAGAGGA	4995
872	UUGGCUUC G CUGCCUUG	199	CAGGGCAG GGCTAGCTACAACGA AGAGCCAA	4996
875	GCUCUGCU G CCCUGUCU	200	AGACAGGG GGCTAGCTACAACGA AGCAGAGC	4997
880	GCUGCCCU G UCUGACCA	201	TGGTCAGA GGCTAGCTACAACGA AGGGCAGC	4998
885	CCUGUCUG A CCAUCCCA	202	TGGGATGG GGCTAGCTACAACGA CAGACAGG	4999
888	GUCUGACC A UCCAGGCC	203	GGCTGGGA GGCTAGCTACAACGA GGTACAGC	5000
894	CCAUCCCA G CCUCCGCU	204	AGCGGAGG GGCTAGCTACAACGA TGGGATGG	5001
900	CAGCCUCC G CUUAUGAG	205	CTCATAAG GGCTAGCTACAACGA GGAGGCTG	5002
904	CUCCGCUU A UGAGGUGU	206	ACACCTCA GGCTAGCTACAACGA AAGCGGAG	5003
909	CUUAUGAG G UGUGCAAC	207	GTTGCACA GGCTAGCTACAACGA CTCATAAG	5004
911	UAUGAGGU G UGCAACGC	208	GCGTTGCA GGCTAGCTACAACGA ACCTCATA	5005
913	UGAGGUGU G CAACGCGU	209	ACGCGTTG GGCTAGCTACAACGA ACACCTCA	5006
916	GGUGUGCA A CGCGUCCG	210	CGGACGCG GGCTAGCTACAACGA TGCACACC	5007
918	UGUGCAAC G CGUCCGGG	211	CCCGGACG GGCTAGCTACAACGA GTTGCACA	5008
920	UGCAACGC G UCCGGGCU	212	AGCCCGGA GGCTAGCTACAACGA GCGTTGCA	5009
926	GCGUCCGG G CUGUACCA	213	TGGTACAG GGCTAGCTACAACGA CCGGACGC	5010
929	UCCGGGCU G UACCAUGU	214	ACATGGTA GGCTAGCTACAACGA AGCCCGGA	5011
931	CGGGCUGU A CCAUGUCA	215	TGACATGG GGCTAGCTACAACGA ACAGCCCG	5012
934	GCUGUACC A UGUCACGA	216	TCGTGACA GGCTAGCTACAACGA GGTACAGC	5013
936	UGUACCAU G UCACGAAC	217	GTTCGTGA GGCTAGCTACAACGA ATGGTACA	5014
939	ACCAUGUC A CGAACGAU	218	ATCGTTGCG GGCTAGCTACAACGA GACATGGT	5015
943	UGUCACGA A CGAUUGCU	219	AGCAATCG GGCTAGCTACAACGA TCGTGACA	5016
946	CACGAACG A UUGCUGCA	220	TGGAGCAA GGCTAGCTACAACGA CGTTCGTG	5017
949	GAACGAUU G CUCCAACU	221	AGTTGGAG GGCTAGCTACAACGA AATCGTTC	5018
955	UUGCUGCA A CUCAAGCA	222	TGCTTGAG GGCTAGCTACAACGA TGGAGCAA	5019
961	CAACUCAA G CAUUGUGU	223	ACACAATG GGCTAGCTACAACGA TTGAGTTG	5020

963	ACUCAAGC A UUGUGUAU	224	ATACACAA GGCTAGCTACAACGA GCTTGAGT	5021
966	CAAGCAUU G UGUUAUGAG	225	CTCATACA GGCTAGCTACAACGA AATGCTTG	5022
968	AGCAUUGU G UAUGAGGC	226	GCCTCATA GGCTAGCTACAACGA ACAATGCT	5023
970	CAUUGUGU A UGAGGCAG	227	CTGCCTCA GGCTAGCTACAACGA ACACAATG	5024
975	UGUAUGAG G CAGAGGAC	228	GTCCCTCTG GGCTAGCTACAACGA CTCATACA	5025
982	GGCAGAGG A CAUGAUCA	229	TGATCATG GGCTAGCTACAACGA CCTCTGCC	5026
984	CAGAGGAC A UGAUCAUG	230	CATGATCA GGCTAGCTACAACGA GTCCTCTG	5027
987	AGGACAUG A UCAUGCAC	231	GTGCATGA GGCTAGCTACAACGA CATGTCTT	5028
990	ACAUGAUC A UGCACACC	232	GGTGTGCA GGCTAGCTACAACGA GATCATGT	5029
992	AUGAUCAU G CACACCCC	233	GGGGTGTG GGCTAGCTACAACGA ATGATCAT	5030
994	GAUCAUGC A CACCCCGG	234	CCGGGGTG GGCTAGCTACAACGA GCATGATC	5031
996	UCAUGCAC A CCCCAGGG	235	CCCCAGGG GGCTAGCTACAACGA GTGCATGA	5032
1004	ACCCCGGG G UGCGUGCC	236	GGCACGCA GGCTAGCTACAACGA CCGGGGGT	5033
1006	CCCGGGGU G CGUGCCCU	237	AGGGCAGG GGCTAGCTACAACGA ACCCCGGG	5034
1008	CGGGGUGC G UGCCCUGC	238	GCAGGGCA GGCTAGCTACAACGA GCACCCCG	5035
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1015	CGUGCCCU G CGUUCGGG	240	CCCGAACG GGCTAGCTACAACGA AGGGCAGG	5037
1017	UGCCCUGC G UUCGGGAG	241	CTCCCGAA GGCTAGCTACAACGA GCAGGGCA	5038
1027	UCGGGAGA A CAACUCCU	242	AGGAGTTG GGCTAGCTACAACGA TCTCCCGA	5039
1030	GGAGAACA A CUCCUCCC	243	GGGAGGAG GGCTAGCTACAACGA TGTTCTCC	5040
1039	CUCCUCCC G CUGCUGGG	244	CCCAGCAG GGCTAGCTACAACGA GGGAGGAG	5041
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1047	GCUGCUGG G UAGCGCUC	246	GAGCGCTA GGCTAGCTACAACGA CCAGCAGC	5043
1050	GCUGGGUA G CGCUCACU	247	AGTGAGCG GGCTAGCTACAACGA TACCCAGC	5044
1052	UGGGUAGC G CUCACUCC	248	GGAGTGAG GGCTAGCTACAACGA GCTACCCA	5045
1056	UAGCGCUC A CUCCCACG	249	CGTGGGAG GGCTAGCTACAACGA GAGCGCTA	5046
1062	UCACUCCC A CGCUCGCG	250	CGCGAGCG GGCTAGCTACAACGA GGGAGTGA	5047
1064	ACUCCCAC G CUCGCGGC	251	GCCGCGAG GGCTAGCTACAACGA GTGGGAGT	5048
1068	CCACGCUC G CGGCCAGG	252	CCTGGCCG GGCTAGCTACAACGA GAGCGTGG	5049
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1080	CCAGGAAU G CCAGCAUC	255	GATGCTGG GGCTAGCTACAACGA ATTCTCTG	5052
1084	GAAUGCCA G CAUCCCCA	256	TGGGGATG GGCTAGCTACAACGA TGGCATTG	5053
1086	AUGCCAGC A UCCCCACU	257	AGTGGGGA GGCTAGCTACAACGA GCTGGCAT	5054
1092	GCAUCCCC A CUACGACG	258	CGTCGTGA GGCTAGCTACAACGA GGGGATGC	5055
1095	UCCCCACU A CGACGAUA	259	TATCGTCT GGCTAGCTACAACGA AGTGGGGA	5056
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1106	ACGAUACG G CGUCACGU	263	ACGTGACG GGCTAGCTACAACGA CGTATCGT	5060
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1137	GGGCGGCU G CUUUCUGC	272	GCAGAAAG GGCTAGCTACAACGA AGCCGCCC	5069
1144	UGC UUUCU G CUCUGCUA	273	TAGCAGAG GGCTAGCTACAACGA AGAAAGCA	5070
1149	UCUGCUCU G CUAUGUAC	274	GTACATAG GGCTAGCTACAACGA AGAGCAGA	5071
1152	GCUCUGCU A UGUACGUG	275	CACGTACA GGCTAGCTACAACGA AGCAGAGC	5072
1154	UCUGCUAU G UACGUGGG	276	CCCACGTA GGCTAGCTACAACGA ATAGCAGA	5073
1156	UGCUAUGU A CGUGGGGG	277	CCCCACG GGCTAGCTACAACGA ACATAGCA	5074
1158	CUAUGUAC G UGGGGGAU	278	ATCCCCCA GGCTAGCTACAACGA GTACATAG	5075
1165	CGUGGGGG A UCUCUGCG	279	CGCAGAGA GGCTAGCTACAACGA CCCCCACG	5076
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1188	UCUUCCUC G UCUCUCAG	283	CTGAGAGA GGCTAGCTACAACGA GAGGAAGA	5080
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1337	GUAUCGCA G UUGCUCG	323	CGGAGCAA GGCTAGCTACAACGA TGCATAC	5120
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1585	CAACGGCA G CUGGCACA	384	TGTGCCAG GGCTAGCTACAACGA TGCCGTTG	5181
1589	GGCAGCUG G CACAUUAA	385	TTAATGTG GGCTAGCTACAACGA CAGCTGCC	5182
1591	CAGCUGGC A CAUUAACA	386	TGTTAATG GGCTAGCTACAACGA GCCAGCTG	5183
1593	GCUGGCAC A UUAACAGG	387	CCTGTTAA GGCTAGCTACAACGA GTGCCAGC	5184
1597	GCACAUUA A CAGGACUG	388	CAGTCCTG GGCTAGCTACAACGA TAATGTGC	5185
1602	UUAACAGG A CUGCCUG	389	CAGGGCAG GGCTAGCTACAACGA CCTGTTAA	5186
1605	ACAGGACU G CCUGAAC	390	GTTCCAGG GGCTAGCTACAACGA AGTCCTGT	5187
1612	UGCCUGA A CUGCAAUG	391	CATTGCAG GGCTAGCTACAACGA TCAGGGCA	5188
1615	CCUGAACU G CAAUGACU	392	AGTCATTG GGCTAGCTACAACGA AGTTCAGG	5189
1618	GAACUGCA A UGACUCCC	393	GGGAGTCA GGCTAGCTACAACGA TGCAGTTC	5190
1621	CUGCAAUG A CUCCUCC	394	GGAGGGAG GGCTAGCTACAACGA CATTGCAG	5191

1632	CCCUCCAA A CCGGGUUC	395	GAACCCGG GGCTAGCTACAACGA TTGGAGGG	5192
1637	CAAACCGG G UUCAUUGC	396	GCAATGAA GGCTAGCTACAACGA CCGGTTTG	5193
1641	CCGGGUUC A UUGCUGCA	397	TGCAGCAA GGCTAGCTACAACGA GAACCCGG	5194
1644	GGUUCAU G CUGCACUG	398	CAGTGCA GGCTAGCTACAACGA AATGAACC	5195
1647	UCAUUGCU G CACUGUUC	399	GAACAGTG GGCTAGCTACAACGA AGCAATGA	5196
1649	AUUGCUGC A CUGUUCUA	400	TAGAACAG GGCTAGCTACAACGA GCAGCAAT	5197
1652	GCUGCACU G UUCUAUGC	401	GCATAGAA GGCTAGCTACAACGA AGTGCAGC	5198
1657	ACUGUUCU A UGCACACA	402	TGTGTGCA GGCTAGCTACAACGA AGAACAGT	5199
1659	UGUUCUAU G CACACAGG	403	CCTGTGTG GGCTAGCTACAACGA ATAGAACA	5200
1661	UUCUAUGC A CACAGGUU	404	AACCTGTG GGCTAGCTACAACGA GCATAGAA	5201
1663	CUAUGCAC A CAGGUUCA	405	TGAACCTG GGCTAGCTACAACGA GTGCATAG	5202
1667	GCACACAG G UUCAACUC	406	GAGTTGAA GGCTAGCTACAACGA CTGTGTGC	5203
1672	CAGGUUCA A CUCGUCCG	407	CGGACGAG GGCTAGCTACAACGA TGAACCTG	5204
1676	UUCAACUC G UCCGGAUG	408	CATCCGGA GGCTAGCTACAACGA GAGTTGAA	5205
1682	UCGUCCGG A UGCCCACA	409	TGTGGGCA GGCTAGCTACAACGA CCGGACGA	5206
1684	GUCCGGAU G CCCACAGC	410	GCTGTGGG GGCTAGCTACAACGA ATCCGGAC	5207
1688	GGAUGCCC A CAGCGCUU	411	AAGCGCTG GGCTAGCTACAACGA GGGCATCC	5208
1691	UGCCCACA G CGCUUGGC	412	GCCAAGCG GGCTAGCTACAACGA TGTGGGCA	5209
1693	CCCACAGC G CUUGGCCA	413	TGGCCAAG GGCTAGCTACAACGA GCTGTGGG	5210
1698	AGCGCUUG G CCAGCUGC	414	GCAGCTGG GGCTAGCTACAACGA CAAGCGCT	5211
1702	CUUGGCCA G CUGCCGCU	415	AGCGGCAG GGCTAGCTACAACGA TGGCCAAG	5212
1705	GGCCAGCU G CCGCUCCA	416	TGGAGCGG GGCTAGCTACAACGA AGCTGGCC	5213
1708	CAGCUGCC G CUCCAUUG	417	CAATGGAG GGCTAGCTACAACGA GGCAGCTG	5214
1713	GCCGCUCC A UUGACAAG	418	CTTGTCAA GGCTAGCTACAACGA GGAGCGGC	5215
1717	CUCCAUUG A CAAGUUCG	419	CGAACTTG GGCTAGCTACAACGA CAATGGAG	5216
1721	AUUGACAA G UUCGCUCA	420	TGAGCGAA GGCTAGCTACAACGA TTGTCAAT	5217
1725	ACAAGUUC G CUCAGGGG	421	CCCCTGAG GGCTAGCTACAACGA GAACTTGT	5218
1733	GCUCAGGG G UGGGUUCC	422	GGACCCCA GGCTAGCTACAACGA CCCTGAGC	5219
1738	GGGGUGGG G UCCUAUCA	423	TGATAGGA GGCTAGCTACAACGA CCCACCCC	5220
1743	GGGGUCCU A UCACCUAC	424	GTAGGTGA GGCTAGCTACAACGA AGGACCCC	5221
1746	GUCCUAUC A CCUACACC	425	GGTGTAGG GGCTAGCTACAACGA GATAGGAC	5222
1750	UAUACCU A ACCGAGG	426	CCTCGTGG GGCTAGCTACAACGA AGGTGATA	5223
1752	UCACCUAC A CCGAGGGC	427	GCCCTCGG GGCTAGCTACAACGA GTAGGTGA	5224
1759	CACCGAGG G CCACAACU	428	AGTTGTGG GGCTAGCTACAACGA CCTCGGTG	5225
1762	CGAGGGCC A CAACUCGG	429	CCGAGTTG GGCTAGCTACAACGA GGCCCTCG	5226
1765	GGGCCACA A CUCGGACC	430	GGTCCGAG GGCTAGCTACAACGA TGTGGCCC	5227
1771	CAACUCGG A CCAGAGGC	431	GCCTCTGG GGCTAGCTACAACGA CCGAGTTG	5228
1778	GACCAGAG G CCCUAUUG	432	CAATAGGG GGCTAGCTACAACGA CTCTGGTC	5229
1783	GAGGCCCU A UUGCUGGC	433	GCCAGCAA GGCTAGCTACAACGA AGGGCCTC	5230
1786	GCCCUAUU G CUGGCACU	434	AGTGCCAG GGCTAGCTACAACGA AATAGGGC	5231
1790	UAUUGCUG G CACUACGC	435	GCGTAGTG GGCTAGCTACAACGA CAGCAATA	5232
1792	UUGCUGGC A CUACGCAC	436	GTGCGTAG GGCTAGCTACAACGA GCCAGCAA	5233
1795	CUGGCACU A CGCACCGC	437	GCGGTGCG GGCTAGCTACAACGA AGTGCCAG	5234
1797	GGCACUAC G CACCGCGG	438	CCGCGGTG GGCTAGCTACAACGA GTAGTGCC	5235
1799	CACUACGC A CCGCGGCC	439	GGCCGCGG GGCTAGCTACAACGA GCGTAGTG	5236
1802	UACGCACC G CGGCCGUG	440	CACGGCCG GGCTAGCTACAACGA GGTGCGTA	5237
1805	GCACCGCG G CCGUGUGG	441	CCACACGG GGCTAGCTACAACGA CGCGGTGC	5238
1808	CCGCGGCC G UGUGUAU	442	ATACCACA GGCTAGCTACAACGA GGCCGCGG	5239
1810	GCGGCCGU G UGUUAUCG	443	CGATACCA GGCTAGCTACAACGA ACGGCCGC	5240
1813	GCCGUGUG G UAUUGUAC	444	GTACGATA GGCTAGCTACAACGA CACACGGC	5241
1815	CGUGUGGU A UCGUACCC	445	GGGTACGA GGCTAGCTACAACGA ACCACACG	5242
1818	GUGGUUAC G UACCCGCA	446	TGCGGGTA GGCTAGCTACAACGA GATACCAC	5243
1820	GGUAUCGU A CCCGCAUC	447	GATGCGGG GGCTAGCTACAACGA ACGATACC	5244
1824	UCGUACCC G CAUCGCAG	448	CTGCGATG GGCTAGCTACAACGA GGGTACGA	5245
1826	GUACCCGC A UCGCAGGU	449	ACCTGCGA GGCTAGCTACAACGA GCGGGTAC	5246
1829	CCCGCAUC G CAGGUAUG	450	CATACCTG GGCTAGCTACAACGA GATGCGGG	5247
1833	CAUCGCAG G UAUGUGGU	451	ACCACATA GGCTAGCTACAACGA CTGCGATG	5248

1835	UCGCAGGU A UGUGGUCC	452	GGACCACA GGCTAGCTACAACGA ACCTGCGA	5249
1837	GCAGGUAU G UGGUCCAG	453	CTGGACCA GGCTAGCTACAACGA ATACCTGC	5250
1840	GGUAUGUG G UCCAGUGU	454	ACACTGGA GGCTAGCTACAACGA CACATACC	5251
1845	GUGGUCCA G UGUUUGC	455	GCAATACA GGCTAGCTACAACGA TGGACCAC	5252
1847	GGUCCAGU G UAUUGCUU	456	AAGCAATA GGCTAGCTACAACGA ACTGGACC	5253
1849	UCCAGUGU A UUGCUUCA	457	TGAAGCAA GGCTAGCTACAACGA ACACTGGA	5254
1852	AGUGUAUU G CUUCACCC	458	GGGTGAAG GGCTAGCTACAACGA AATACACT	5255
1857	AUUGCUUC A CCCCAAGC	459	GCTTGGGG GGCTAGCTACAACGA GAAGCAAT	5256
1864	CACCCCAA G CCCUGUUG	460	CAACAGGG GGCTAGCTACAACGA TTGGGGTG	5257
1869	CAAGCCCU G UUGUGGUG	461	CACCACAA GGCTAGCTACAACGA AGGGCTTG	5258
1872	GCCCUGUU G UGGUGGGG	462	CCCCACCA GGCTAGCTACAACGA AACAGGGC	5259
1875	CUGUUGUG G UGGGGACG	463	CGTCCCCA GGCTAGCTACAACGA CACAACAG	5260
1881	UGGUGGGG A CGACCGAC	464	GTCGGTCG GGCTAGCTACAACGA CCCCACCA	5261
1884	UGGGGACG A CCGACCGU	465	ACGGTCGG GGCTAGCTACAACGA CGTCCCCA	5262
1888	GACGACCG A CCGUUUCG	466	CGAAACGG GGCTAGCTACAACGA CGGTCGTC	5263
1891	GACCGACC G UUUCGGCG	467	CGCCGAAA GGCTAGCTACAACGA GGTTCGGTC	5264
1897	CCGUUUCG G CGCCCCCA	468	TGGGGGCG GGCTAGCTACAACGA CGAAACGG	5265
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1905	GCGCCCCC A CGUAUAAC	470	GTTATACG GGCTAGCTACAACGA GGGGGCGC	5267
1907	GCCCCCAC G UAUAACUG	471	CAGTTATA GGCTAGCTACAACGA GTGGGGGC	5268
1909	CCCCACGU A UAACUGGG	472	CCCAGTTA GGCTAGCTACAACGA ACGTGGGG	5269
1912	CACGUUAU A CUGGGGGG	473	CCCCCAG GGCTAGCTACAACGA TATACGTG	5270
1920	ACUGGGGG G CGAACGAG	474	CTCGTTCG GGCTAGCTACAACGA CCCCCAGT	5271
1924	GGGGGCGA A CGAGACGG	475	CCGTCTCG GGCTAGCTACAACGA TCGCCCCC	5272
1929	CGAACGAG A CGGACGUG	476	CACGTCCG GGCTAGCTACAACGA CTCGTTCTG	5273
1933	CGAGACGG A CGUGCUGC	477	GCAGCACG GGCTAGCTACAACGA CCGTCTCG	5274
1935	AGACGGAC G UGUCGUC	478	GAGCAGCA GGCTAGCTACAACGA GTCCGTCT	5275
1937	ACGGACGU G CUGCUCCU	479	AGGAGCAG GGCTAGCTACAACGA ACGTCCGT	5276
1940	GACGUGCU G CUCCUCAA	480	TTGAGGAG GGCTAGCTACAACGA AGCACGTC	5277
1948	GCUCCUCA A CAACACGC	481	GCGTGTG GGCTAGCTACAACGA TGAGGAGC	5278
1951	CCUCAACA A CACGCGGC	482	GCCGCGTG GGCTAGCTACAACGA TGTGAGG	5279
1953	UCAACAAC A CGCGCGCG	483	CGGCGCGG GGCTAGCTACAACGA GTTGTGTA	5280
1955	AACAACAC G CGCGCGCC	484	GGCGCGCG GGCTAGCTACAACGA GTGTTGTT	5281
1958	AACACGCG G CCGCCGCA	485	TGCGCGCG GGCTAGCTACAACGA CGCGTGT	5282
1961	ACGCGGCC G CCGCAAGG	486	CCTTGCGG GGCTAGCTACAACGA GGCCGCGT	5283
1964	CGGCCGCC G CAAGGCAA	487	TTGCCTTG GGCTAGCTACAACGA GCGGCCG	5284
1969	GCCGCAAG G CAACUGGU	488	ACCAGTTG GGCTAGCTACAACGA CTTGCGGC	5285
1972	GCAAGGCA A CUGGUUCG	489	CGAACCAG GGCTAGCTACAACGA TGCCTTGC	5286
1976	GGCAACUG G UUCGGCUG	490	CAGCCGAA GGCTAGCTACAACGA CAGTTGCC	5287
1981	CUGGUUCG G CUGCAU	491	ATGTGCAG GGCTAGCTACAACGA CGAACCAG	5288
1984	GUUCGGCU G CACAUGGA	492	TCCATGTG GGCTAGCTACAACGA AGCCGAAC	5289
1986	UCGGCUGC A CAUGGAUG	493	CATCCATG GGCTAGCTACAACGA GCAGCCGA	5290
1988	GGCUGCAC A UGGAUGAA	494	TTCATCCA GGCTAGCTACAACGA GTGCAGCC	5291
1992	GCACAUGG A UGAAUGGC	495	GCCATTCA GGCTAGCTACAACGA CCATGTGC	5292
1996	AUGGAUGA A UGGCACUG	496	CAGTGCCA GGCTAGCTACAACGA TCATCCAT	5293
1999	GAUGAAUG G CACUGGGU	497	ACCCAGTG GGCTAGCTACAACGA CATTTCAT	5294
2001	UGAAUGGC A CUGGGUUC	498	GAACCCAG GGCTAGCTACAACGA GCCATTCA	5295
2006	GGCACUGG G UUCACCAA	499	TTGTTGAA GGCTAGCTACAACGA CCAGTGCC	5296
2010	CUGGGUUC A CCAAGACG	500	CGTCTTGG GGCTAGCTACAACGA GAACCCAG	5297
2016	UCACCAAG A CGUGCGGG	501	CCCGCACG GGCTAGCTACAACGA CTTGGTGA	5298
2018	ACCAAGAC G UGCGGGGG	502	CCCCCGCA GGCTAGCTACAACGA GTCTTGGT	5299
2020	CAAGACGU G CGGGGGCC	503	GGCCCCCG GGCTAGCTACAACGA ACGTCTTG	5300
2026	GUGCGGGG G CCCCCCGU	504	ACGGGGGG GGCTAGCTACAACGA CCCCAC	5301
2033	GGCCCCC G UGCAACAU	505	ATGTTGCA GGCTAGCTACAACGA GGGGGGCC	5302
2035	CCCCCGU G CAACAUCG	506	CGATGTTG GGCTAGCTACAACGA ACGGGGGG	5303
2038	CCCCGCA A CAUCGGGG	507	CCCCGATG GGCTAGCTACAACGA TGCACGGG	5304
2040	CGUGCAAC A UCGGGGGG	508	CCCCCGA GGCTAGCTACAACGA GTTGCACG	5305

2049	UCGGGGGG G CCGGUAAC	509	GTTACCGG GGCTAGCTACAACGA CCCCCGA	5306
2053	GGGGGCCG G UAACGACA	510	TGTCGTTA GGCTAGCTACAACGA CGGCCCCC	5307
2056	GGCCGGUA A CGACACCU	511	AGGTGTCG GGCTAGCTACAACGA TACCGGCC	5308
2059	CGGUAACG A CACCUUAA	512	TTAAGGTG GGCTAGCTACAACGA CGTTACCG	5309
2061	GUAACGAC A CCUUAACC	513	GGTTAAGG GGCTAGCTACAACGA GTCGTTAC	5310
2067	ACACCUUA A CCUGCCCC	514	GGGGCAGG GGCTAGCTACAACGA TAAGGTGT	5311
2071	CUUAACCU G CCCACGG	515	CCGTGGGG GGCTAGCTACAACGA AGGTAAAG	5312
2076	CCUGCCCC A CGGACUGC	516	GCAGTCCG GGCTAGCTACAACGA GGGGCAGG	5313
2080	CCCACGG A CUGCUUCC	517	GGAAGCAG GGCTAGCTACAACGA CCGTGGGG	5314
2083	CACGGACU G CUUCCGGA	518	TCCGGAAG GGCTAGCTACAACGA AGTCCGTG	5315
2093	UUCCGGAA G CACCCCGA	519	TCGGGGTG GGCTAGCTACAACGA TTCCGGAA	5316
2095	CCGGAAGC A CCCCAGG	520	CCTCGGGG GGCTAGCTACAACGA GCTTCCGG	5317
2103	ACCCCGAG G CCACUAC	521	GTAAGTGG GGCTAGCTACAACGA CTCGGGGT	5318
2106	CCGAGGCC A CUUACGCA	522	TGCGTAAG GGCTAGCTACAACGA GGCTCGG	5319
2110	GGCCACUU A CGCAAAGU	523	ACTTTGCG GGCTAGCTACAACGA AAGTGGCC	5320
2112	CCACUAC G CAAAGUGC	524	GCACTTTG GGCTAGCTACAACGA GTAAGTGG	5321
2117	UACGCAA G UGCGGUUC	525	GAACCGCA GGCTAGCTACAACGA TTTGCGTA	5322
2119	CGCAAAGU G CGGUUCGG	526	CCGAACCG GGCTAGCTACAACGA ACTTTGCG	5323
2122	AAAGUGCG G UUCGGGGC	527	GCCCCGAA GGCTAGCTACAACGA CGCACTTT	5324
2129	GGUUCGGG G CCUUGGUU	528	AACCAAGG GGCTAGCTACAACGA CCCGAACC	5325
2135	GGGCCUUG G UUAACACC	529	GGTGTAA GGCTAGCTACAACGA CAAGGCC	5326
2139	CUUGGUUA A CACCUAGA	530	TCTAGGTG GGCTAGCTACAACGA TAACCAAG	5327
2141	UGGUUAAC A CCUAGAUG	531	CATCTAGG GGCTAGCTACAACGA GTTAACCA	5328
2147	ACACCUAG A UGCAUAGU	532	ACTATGCA GGCTAGCTACAACGA CTAGGTGT	5329
2149	ACCUAGAU G CAUAGUUG	533	CAACTATG GGCTAGCTACAACGA ATCTAGGT	5330
2151	CUAGAUGC A UAGUUGAC	534	GTCAACTA GGCTAGCTACAACGA GCATCTAG	5331
2154	GAUGCAUA G UUGACUAC	535	GTAGTCAA GGCTAGCTACAACGA TATGCATC	5332
2158	CAUAGUUG A CUACCAU	536	ATGGGTAG GGCTAGCTACAACGA CAACTATG	5333
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2179	GCUUUGGC A CUACCCU	542	AGGGTAG GGCTAGCTACAACGA GCCAAAGC	5339
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2188	CUACCCU G CACUGUCA	544	TGACAGTG GGCTAGCTACAACGA AGGGGTAG	5341
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2193	CCUGCACU G UCAAUUU	546	AAAATTGA GGCTAGCTACAACGA AGTGCAGG	5343
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2214	UCUUUAAG G UUAGGAUG	549	CATCCTAA GGCTAGCTACAACGA CTTAAAGA	5346
2220	AGGUUAGG A UGUUUGUG	550	CACATACA GGCTAGCTACAACGA CCTAACCT	5347
2222	GUUAGGAU G UAUGUGG	551	CCCACATA GGCTAGCTACAACGA ATCCTAAC	5348
2224	UAGGAUGU A UGUGGGG	552	CCCCACA GGCTAGCTACAACGA ACATCCTA	5349
2226	GGAUGUAU G UGGGGGC	553	GCCCCCA GGCTAGCTACAACGA ATACATCC	5350
2233	UGUGGGGG G CGUGGAGC	554	GCTCCACG GGCTAGCTACAACGA CCCCCACA	5351
2235	UGGGGGGC G UGGAGCAC	555	GTGCTCCA GGCTAGCTACAACGA GCCCCCA	5352
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2242	CGUGGAGC A CAGGCUCA	557	TGAGCCTG GGCTAGCTACAACGA GCTCCACG	5354
2246	GAGCACAG G CUCACCGC	558	GCGGTGAG GGCTAGCTACAACGA CTGTGCTC	5355
2250	ACAGGCUC A CCGCCGCA	559	TGCGGCGG GGCTAGCTACAACGA GAGCCTGT	5356
2253	GGCUCACC G CCGCAUGC	560	GCATGCGG GGCTAGCTACAACGA GGTGAGCC	5357
2256	UCACCGCC G CAUGCAAU	561	ATTGCAATG GGCTAGCTACAACGA GCGGTGA	5358
2258	ACCGCCG A UGCAAUUG	562	CAATTGCA GGCTAGCTACAACGA GCGGCGGT	5359
2260	CGCCGCAU G CAAUUGGA	563	TCCAATTG GGCTAGCTACAACGA ATGCGGCG	5360
2263	CGCAUGCA A UUGGACUC	564	GAGTCCAA GGCTAGCTACAACGA TGCATGCG	5361
2268	GCAAUUGG A CUCGAGGA	565	TCCTCGAG GGCTAGCTACAACGA CCAATTGC	5362

2279	CGAGGAGA G CGUUGUGA	566	TCACAACG GGCTAGCTACAACGA TCTCCTCG	5363
2281	AGGAGAGC G UUGUGAUU	567	AATCACAA GGCTAGCTACAACGA GCTCTCCT	5364
2284	AGAGCGUU G UGAUUUGG	568	CCAAATCA GGCTAGCTACAACGA AACGCTCT	5365
2287	GCGUUGUG A UUUGGAGG	569	CCTCCAAA GGCTAGCTACAACGA CACAACGC	5366
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2306	AGGGACAG A UCAGAGCU	572	AGCTCTGA GGCTAGCTACAACGA CTGTCCCT	5369
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2317	AGAGCUCA G CCCGCGC	574	GCAGCGGG GGCTAGCTACAACGA TGAGCTCT	5371
2321	CUCAGCCC G CUGCUGUU	575	AACAGCAG GGCTAGCTACAACGA GGGTGAG	5372
2324	AGCCCGCU G CUGUUGUC	576	GACAACAG GGCTAGCTACAACGA AGCGGGCT	5373
2327	CCGCUGCU G UUGUCCAC	577	GTGGACAA GGCTAGCTACAACGA AGCAGCGG	5374
2330	CUGCUGUU G UCCACUAC	578	GTAGTGGA GGCTAGCTACAACGA AACAGCAG	5375
2334	UGUUGUCC A CUACAGAG	579	CTCTGTAG GGCTAGCTACAACGA GGACAACA	5376
2337	UGUCCACU A CAGAGUGG	580	CCACTCTG GGCTAGCTACAACGA AGTGGACA	5377
2342	ACUACAGA G UGGCAAAU	581	ATTTGCCA GGCTAGCTACAACGA TCTGTAGT	5378
2345	ACAGAGUG G CAAAUACU	582	AGTATTTG GGCTAGCTACAACGA CACTCTGT	5379
2349	AGUGGCAA A UACUGCCC	583	GGGCAGTA GGCTAGCTACAACGA TTGCCACT	5380
2351	UGGCAAAU A CUGCCUG	584	CAGGGCAG GGCTAGCTACAACGA ATTTGCCA	5381
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2370	CCUUCACC A CCCUACCG	588	CGGTAGGG GGCTAGCTACAACGA GGTGAAGG	5385
2375	ACCACCCU A CCGGCUCU	589	AGAGCCGG GGCTAGCTACAACGA AGGGTGGT	5386
2379	CCCUACCG G CUCUGUCC	590	GGACAGAG GGCTAGCTACAACGA CGGTAGGG	5387
2384	CCGGCUCU G UCCACUGG	591	CCAGTGGA GGCTAGCTACAACGA AGAGCCGG	5388
2388	CUCUGUCC A CUGGUUUG	592	CAAACCAG GGCTAGCTACAACGA GGACAGAG	5389
2392	GUCCACUG G UUGAUCC	593	GGATCAAA GGCTAGCTACAACGA CAGTGGAC	5390
2397	CUGGUUUG A UCCAUCUC	594	GAGATGGA GGCTAGCTACAACGA CAAACCAG	5391
2401	UUUGAUCC A UCUCACC	595	GGTGGAGA GGCTAGCTACAACGA GGATCAAA	5392
2407	CCAUCUCC A CCAGAACA	596	TGTTCTGG GGCTAGCTACAACGA GGAGATGG	5393
2413	CCACCAGA A CAUCGUGG	597	CCACGATG GGCTAGCTACAACGA TCTGGTGG	5394
2415	ACCAGAAC A UCGUGGAC	598	GTCCACGA GGCTAGCTACAACGA GTTCTGGT	5395
2418	AGAACAUC G UGACGUG	599	CACGTCCA GGCTAGCTACAACGA GATGTTCT	5396
2422	CAUCGUGG A CGUGCAAU	600	ATTGCACG GGCTAGCTACAACGA CCACGATG	5397
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2426	GUGGACGU G CAAUACCU	602	AGGTATTG GGCTAGCTACAACGA ACGTCCAC	5399
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2435	CAAUACCU G UACGGUGU	605	ACACCGTA GGCTAGCTACAACGA AGGTATTG	5402
2437	AUACCUGU A CGGUGUAG	606	CTACACCG GGCTAGCTACAACGA ACAGGTAT	5403
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2447	GGUGUAGG G UCAGCGGU	609	ACCGCTGA GGCTAGCTACAACGA CCTACACC	5406
2451	UAGGGUCA G CGGUUGUC	610	GACAACCG GGCTAGCTACAACGA TGACCCTA	5407
2454	GGUCAGCG G UUGUCUCC	611	GGAGACAA GGCTAGCTACAACGA CGCTGACC	5408
2457	CAGCGGUU G UCUCUUC	612	GAAGGAGA GGCTAGCTACAACGA AACCCTG	5409
2466	UCUCUUC G CAAUCAA	613	TTTGATTG GGCTAGCTACAACGA GAAGGAGA	5410
2469	CCUUCGCA A UCAAAUGG	614	CCATTGTA GGCTAGCTACAACGA TGCGAAGG	5411
2474	GCAAUCAA A UGGGAGUA	615	TACTCCCA GGCTAGCTACAACGA TTGATTGC	5412
2480	AAAUUGGA G UAUGUCCU	616	AGGACATA GGCTAGCTACAACGA TCCCATT	5413
2482	AUGGGAGU A UGUCCUGU	617	ACAGGACA GGCTAGCTACAACGA ACTCCCAT	5414
2484	GGGAGUAU G UCCUGUUG	618	CAACAGGA GGCTAGCTACAACGA ATACTCCC	5415
2489	UAUGUCCU G UUGCUUUU	619	AAAAGCAA GGCTAGCTACAACGA AGGACATA	5416
2492	GUCCUGUU G CUUUUCCU	620	AGGAAAAG GGCTAGCTACAACGA AACAGGAC	5417
2508	UUCUCCUG G CAGACGCG	621	CGCGTCTG GGCTAGCTACAACGA CAGGAGAA	5418
2512	CCUGGCAG A CGCGCGCG	622	CGCGCGCG GGCTAGCTACAACGA CTGCCAGG	5419

2514	UGGCAGAC G CGCGCGUC	623	GACGCGCG GGCTAGCTACAACGA GTCTGCCA	5420
2516	GCAGACGC G CGCGUCUG	624	CAGACGCG GGCTAGCTACAACGA GCGTCTGC	5421
2518	AGACGCGC G CGUCUGUG	625	CACAGACG GGCTAGCTACAACGA GCGCGTCT	5422
2520	ACGCGCGC G UCUGUGCC	626	GGCACAGA GGCTAGCTACAACGA GCGCGCGT	5423
2524	GCGCGUCU G UGCCUGUU	627	AACAGGCA GGCTAGCTACAACGA AGACGCGC	5424
2526	GCGUCUGU G CCUGUUUG	628	CAACACAG GGCTAGCTACAACGA ACAGACGC	5425
2530	CUGUGCCU G UUUGUGGA	629	TCCACAAA GGCTAGCTACAACGA AGGCACAG	5426
2534	GCCUGUUU G UGGAUGAU	630	ATCATCCA GGCTAGCTACAACGA AAACAGGC	5427
2538	GUUUGUGG A UGAUGCUG	631	CAGCATCA GGCTAGCTACAACGA CCACAAAC	5428
2541	UGUGGAUG A UGCUUGUG	632	CAACAGCA GGCTAGCTACAACGA CATCCACA	5429
2543	UGGAUGAU G CUGUUGGU	633	ACCAACAG GGCTAGCTACAACGA ATCATCCA	5430
2546	AUGAUGCU G UUGGUAGC	634	GCTACCAA GGCTAGCTACAACGA AGCATCAT	5431
2550	UGCUGUUG G UAGCCCAG	635	CTGGGCTA GGCTAGCTACAACGA CAACAGCA	5432
2553	UGUUGGUA G CCCAGGCC	636	GGCCTGGG GGCTAGCTACAACGA TACCAACA	5433
2559	UAGCCCAG G CCGAGGCU	637	AGCCTCGG GGCTAGCTACAACGA CTGGGCTA	5434
2565	AGGCCGAG G CUGCCCUA	638	TAGGGCAG GGCTAGCTACAACGA CTCGGCCT	5435
2568	CCGAGGCU G CCCUAGAG	639	CTCTAGGG GGCTAGCTACAACGA AGCCTCGG	5436
2578	CCUAGAGA A CCUGGUGG	640	CCACCAGG GGCTAGCTACAACGA TCTCTAGG	5437
2583	AGAACCUG G UGUCCUC	641	GAGGACCA GGCTAGCTACAACGA CAGGTTCT	5438
2586	ACCUGGUG G UCCUCAAU	642	ATTGAGGA GGCTAGCTACAACGA CACCAGGT	5439
2593	GGUCCUCA A UGCAGCAU	643	ATGCTGCA GGCTAGCTACAACGA TGAGGACC	5440
2595	UCCUCAAU G CAGCAUCC	644	GGATGCTG GGCTAGCTACAACGA ATTGAGGA	5441
2598	UCAAUACA G CAUCCUUG	645	CAAGGATG GGCTAGCTACAACGA TGCATTGA	5442
2600	AAUGCAGC A UCCUUGGC	646	GCCAAGGA GGCTAGCTACAACGA GCTGCATT	5443
2607	CAUCCUUG G CCGGAGUG	647	CACTCCGG GGCTAGCTACAACGA CAAGGATG	5444
2613	UGGCCGGA G UGCAUGGC	648	GCCATGCA GGCTAGCTACAACGA TCCGGCCA	5445
2615	GCCGGAGU G CAUGGCAU	649	ATGCCATG GGCTAGCTACAACGA ACTCCGGC	5446
2617	CGGAGUGC A UGGCAUCC	650	GGATGCCA GGCTAGCTACAACGA GCACTCCG	5447
2620	AGUGCAUG G CAUCCUCU	651	AGAGGATG GGCTAGCTACAACGA CATGCACT	5448
2622	UGCAUGGC A UCCUCUCC	652	GGAGAGGA GGCTAGCTACAACGA GCCATGCA	5449
2637	CCUUCUCU G UGUUCUUC	653	GAAGAACA GGCTAGCTACAACGA GAGGAAGG	5450
2639	UUCUCUGU G UUCUUCUG	654	CAGAAGAA GGCTAGCTACAACGA ACGAGGAA	5451
2647	GUUCUUCU G UGUGCCU	655	AGGCAGCA GGCTAGCTACAACGA AGAAGAAC	5452
2649	UCUUCUGU G CUGCCUGG	656	CCAGGCA GGCTAGCTACAACGA ACAGAAGA	5453
2652	UCUGUGCU G CCUGGUAC	657	GTACCAGG GGCTAGCTACAACGA AGCACAGA	5454
2657	GCUGCCUG G UACAUCAA	658	TTGATGTA GGCTAGCTACAACGA CAGGCAGC	5455
2659	UGCCUGGU A CAUCAAAG	659	CTTTGATG GGCTAGCTACAACGA ACCAGCA	5456
2661	CCUGGUAC A UCAAAGGC	660	GCCTTTGA GGCTAGCTACAACGA GTACCAGG	5457
2668	CAUCAAAG G CAAGCUGG	661	CCAGCTTG GGCTAGCTACAACGA CTTTGATG	5458
2672	AAAGGCAA G CUGGUCCC	662	GGGACCAG GGCTAGCTACAACGA TTGCCTTT	5459
2676	GCAAGCUG G UCCUGGG	663	CCCAGGGA GGCTAGCTACAACGA CAGCTTGC	5460
2685	UCCUGGG G CGGCAUUA	664	ATATGCCG GGCTAGCTACAACGA CCCAGGGA	5461
2688	CUGGGGCG G CAUAUGCU	665	AGCATATG GGCTAGCTACAACGA CGCCCCAG	5462
2690	GGGGCGGC A UAUGCUCU	666	AGAGCATA GGCTAGCTACAACGA GCCGCCCC	5463
2692	GGCGCAU A UGCUCUCU	667	AGAGAGCA GGCTAGCTACAACGA ATGCCGCC	5464
2694	CGGCAUUA G CUCUCUAC	668	GTAGAGAG GGCTAGCTACAACGA ATATGCCG	5465
2701	UGCUCUCU A CGGCGUAU	669	ATACGCCG GGCTAGCTACAACGA AGAGAGCA	5466
2704	UCUCUACG G CGUAUGGC	670	GCCATACG GGCTAGCTACAACGA CGTAGAGA	5467
2706	UCUACGGC G UAUGGCCG	671	CGGCCATA GGCTAGCTACAACGA GCCGTAGA	5468
2708	UACGGCGU A UGGCCGCU	672	AGCGCCA GGCTAGCTACAACGA ACGCCGTA	5469
2711	GGCGUAUG G CCGCUACU	673	AGTAGCGG GGCTAGCTACAACGA CATACGCC	5470
2714	GUAUGGCC G CUACUCCU	674	AGGAGTAG GGCTAGCTACAACGA GGCCATAC	5471
2717	UGGCCGCU A CUCCUGCU	675	AGCAGGAG GGCTAGCTACAACGA AGCGGCCA	5472
2723	CUACUCCU G CUCCUGCU	676	AGCAGGAG GGCTAGCTACAACGA AGGAGTAG	5473
2729	CUGCUCCU G CUGGCGUU	677	AACGCCAG GGCTAGCTACAACGA AGGAGCAG	5474
2733	UCCUGCUG G CGUUACCA	678	TGGTAACG GGCTAGCTACAACGA CAGCAGGA	5475
2735	CUGCUGGC G UUACCACC	679	GGTGGTAA GGCTAGCTACAACGA GCCAGCAG	5476

2738	CUGGCGUU A CCACCACG	680	CGTGGTGG GGCTAGCTACAACGA AACGCCAG	5477
2741	GCGUUAAC A CCACGGGC	681	GCCCGTGG GGCTAGCTACAACGA GGTAACGC	5478
2744	UUACCACC A CGGGCGUA	682	TACGCCCG GGCTAGCTACAACGA GGTGGTAA	5479
2748	CACCACGG G CGUACGCC	683	GGCGTACG GGCTAGCTACAACGA CCGTGGTG	5480
2750	CCACGGGC G UACGCCAU	684	ATGGCGTA GGCTAGCTACAACGA GCCCGTGG	5481
2752	ACGGGCGU A CGCCAUGG	685	CCATGGCG GGCTAGCTACAACGA ACGCCCGT	5482
2754	GGGCGUAC G CCAUGGAC	686	GTCCATGG GGCTAGCTACAACGA GTACGCC	5483
2757	CGUACGCC A UGGACCGG	687	CCGGTCCA GGCTAGCTACAACGA GCGGTACG	5484
2761	CGCCAUGG A CCGGGAGA	688	TCTCCCGG GGCTAGCTACAACGA CCATGGCG	5485
2769	ACCGGGAG A UGGCCGCA	689	TGCGGCCA GGCTAGCTACAACGA CTCCCGGT	5486
2772	GGGAGAUG G CCGCAUCG	690	CGATGCGG GGCTAGCTACAACGA CATCTCCC	5487
2775	AGAUGGCC G CAUCGUGC	691	GCACGATG GGCTAGCTACAACGA GGCCATCT	5488
2777	AUGGCCGC A UCGUGCGG	692	CCGCACGA GGCTAGCTACAACGA GCGGCCAT	5489
2780	GCCGCAUC G UGCGGAGG	693	CCTCCGCA GGCTAGCTACAACGA GATGCGGC	5490
2782	CGCAUCGU G CGGAGGCG	694	CGCCTCCG GGCTAGCTACAACGA ACGATGCG	5491
2788	GUGCGGAG G CGUGGUUU	695	AAACCACG GGCTAGCTACAACGA CTCCGCAC	5492
2790	GCGGAGGC G UGUUUUUU	696	AAAAACCA GGCTAGCTACAACGA GCCTCCGC	5493
2793	GAGGCGUG G UUUUUGUA	697	TACAAAAA GGCTAGCTACAACGA CACGCCTC	5494
2799	UGGUUUUU G UAGGUCUA	698	TAGACCTA GGCTAGCTACAACGA AAAAACCA	5495
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2808	UAGGUCUA G CACUCUUG	700	CAAGAGTG GGCTAGCTACAACGA TAGACCTA	5497
2810	GGUCUAGC A CUCUUGAC	701	GTCAAGAG GGCTAGCTACAACGA GCTAGACC	5498
2817	CACUCUUG A CCUUGUCA	702	TGACAAGG GGCTAGCTACAACGA CAAGAGTG	5499
2822	UUGACCUU G UCACCAUA	703	TATGGTGA GGCTAGCTACAACGA AAGGTCAA	5500
2825	ACCUUGUC A CCAUACUA	704	TAGTATGG GGCTAGCTACAACGA GACAAGGT	5501
2828	UUGUCACC A UACUACAA	705	TTGTAGTA GGCTAGCTACAACGA GGTGACAA	5502
2830	GUCACCAU A CUACAAAG	706	CTTTGTAG GGCTAGCTACAACGA ATGGTGAC	5503
2833	ACCAUACU A CAAAGUGU	707	ACACTTTG GGCTAGCTACAACGA AGTATGGT	5504
2838	ACUACAAA G UGUUCCUC	708	GAGGAACA GGCTAGCTACAACGA TTTGTAGT	5505
2840	UACAAAGU G UUCUCGCG	709	GCGAGGAA GGCTAGCTACAACGA ACTTTGTA	5506
2847	UGUUCUC G CUAGGCUC	710	GAGCCTAG GGCTAGCTACAACGA GAGGAACA	5507
2852	CUCGCUAG G CUCAUAUG	711	CATATGAG GGCTAGCTACAACGA CTAGCGAG	5508
2856	CUAGGCUC A UAUUGUGG	712	CCACCATA GGCTAGCTACAACGA GAGCCTAG	5509
2858	AGGCUCAU A UGGUGGUU	713	AACCACCA GGCTAGCTACAACGA ATGAGCCT	5510
2861	CUCAUAUG G UGUUGCA	714	TGCAACCA GGCTAGCTACAACGA CATATGAG	5511
2864	AUAUGGUG G UUGCAUA	715	TATTGCAA GGCTAGCTACAACGA CACCATAT	5512
2867	UGGUGGUU G CAAUACCU	716	AGGTATTE GGCTAGCTACAACGA AACCACCA	5513
2870	UGGUUGCA A UACCUUAU	717	ATAAGGTA GGCTAGCTACAACGA TGCAACCA	5514
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2880	ACCUUAUC A CCAGAGCC	720	GGCTCTGG GGCTAGCTACAACGA GATAAGGT	5517
2886	UCACCAGA G CCGAGGCG	721	CGCCTCGG GGCTAGCTACAACGA TCTGGTGA	5518
2892	GAGCCGAG G CGCAGUUG	722	CAACTGCG GGCTAGCTACAACGA CTCGGCTC	5519
2894	GCCGAGGC G CAGUUGCA	723	TGCAACTG GGCTAGCTACAACGA GCCTCGGC	5520
2897	GAGGCGCA G UUGCAAGU	724	ACTTGCAA GGCTAGCTACAACGA TGCGCCTC	5521
2900	GCGCAGUU G CAAGUGUG	725	CACACTTG GGCTAGCTACAACGA AACTGCGC	5522
2904	AGUUGCAA G UGUGGAUC	726	GATCCACA GGCTAGCTACAACGA TTGCAACT	5523
2906	UUGCAAGU G UGGAUCCC	727	GGGATCCA GGCTAGCTACAACGA ACTTGCAA	5524
2910	AAGUGUGG A UCCCCCCC	728	GGGGGGGA GGCTAGCTACAACGA CCACACTT	5525
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2938	GGGGGGGG G CGUGCCA	732	TGGCACCG GGCTAGCTACAACGA GCCCCCCC	5529
2941	GGGGCGCG G UGCCAUCA	733	TGATGGCA GGCTAGCTACAACGA CGCGCCCC	5530
2943	GGCGCGGU G CCAUCAUU	734	AATGATGG GGCTAGCTACAACGA ACCGCGCC	5531
2946	GCGGUGCC A UCAUUCUC	735	GAGAATGA GGCTAGCTACAACGA GGCACCGC	5532
2949	GUGCCAUC A UUCUCCUC	736	GAGGAGAA GGCTAGCTACAACGA GATGGCAC	5533

2958	UUCUCCUC A CGUGUGUG	737	CACACACG GGCTAGCTACAACGA GAGGAGAA	5534
2960	CUCCUCAC G UGUGUGGU	738	ACCACACA GGCTAGCTACAACGA GTGAGGAG	5535
2962	CCUCACGU G UGUGGUCC	739	GGACCACA GGCTAGCTACAACGA ACGTGAGG	5536
2964	UCACGUGU G UGUCCAC	740	GTGGACCA GGCTAGCTACAACGA ACACGTGA	5537
2967	CGUGUGUG G UCCACCCA	741	TGGGTGGA GGCTAGCTACAACGA CACACACG	5538
2971	UGUGGUCC A CCCAGAGC	742	GCTCTGGG GGCTAGCTACAACGA GGACCACA	5539
2978	CACCCAGA G CUAUUCUU	743	AAGATTAG GGCTAGCTACAACGA TCTGGGTG	5540
2982	CAGAGCUA A UCUUUGAC	744	GTCAAAGA GGCTAGCTACAACGA TAGCTCTG	5541
2989	AAUCUUUG A CAUCACCA	745	TGGTGATG GGCTAGCTACAACGA CAAAGATT	5542
2991	UCUUUGAC A UCACCAA	746	TTTGGTGA GGCTAGCTACAACGA GTCAAAGA	5543
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3005	AAAAUUU G CUCGCCAU	750	ATGGCGAG GGCTAGCTACAACGA ATAATTTT	5547
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3019	CAUACUCG G CCCGCUCA	754	TGAGCGGG GGCTAGCTACAACGA CGAGTATG	5551
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3027	GCCCGCUC A UGUGGCUC	756	GAGCACC A GGCTAGCTACAACGA GAGCGGGC	5553
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3032	CUCAUGGU G CUCCAGGC	758	GCCTGGAG GGCTAGCTACAACGA ACCATGAG	5555
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3168	UGAAAGGU A CGUCCGUC	790	GACGGACG GGCTAGCTACAACGA ACCTTTCA	5587
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3189	ACCACCUC A CUCCACUG	796	CAGTGGAG GGCTAGCTACAACGA GAGGTGGT	5593
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3226	UCUACGAG A CCUGGCGG	805	CCGCCAGG GGCTAGCTACAACGA CTCGTAGA	5602
3231	GAGACCUG G CGGUAGCG	806	CGCTACCG GGCTAGCTACAACGA CAGGTCTC	5603
3234	ACCUGGCG G UAGCGGUC	807	GACCGCTA GGCTAGCTACAACGA CGCCAGGT	5604
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3240	CGGUAGCG G UCGAGCCC	809	GGGCTCGA GGCTAGCTACAACGA CGCTACCG	5606
3245	GCGGUCGA G CCCGUCGU	810	ACGACGGG GGCTAGCTACAACGA TCGACCGC	5607
3249	UCGAGCCC G UCGUCUUC	811	GAAGACGA GGCTAGCTACAACGA GGGCTCGA	5608
3252	AGCCCGUC G UCUUCUCC	812	GGAGAAGA GGCTAGCTACAACGA GACGGGCT	5609
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3264	UCUCCGAC A UGGAUAUC	814	GATTTCCA GGCTAGCTACAACGA GTCGGAGA	5611
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3276	AAAUCAAG A UCAUACC	816	GGTGATGA GGCTAGCTACAACGA CTTGATTT	5613
3279	UCAAGAUC A UCACCUGG	817	CCAGGTGA GGCTAGCTACAACGA GATCTTGA	5614
3282	AGAUCAUC A CCUGGGGG	818	CCCCCAGG GGCTAGCTACAACGA GATGATCT	5615
3295	GGGGGGAG A CACCGCGG	819	CCGCGGTG GGCTAGCTACAACGA CTCCCCC	5616
3297	GGGGAGAC A CCGCGGCG	820	CGCCGCGG GGCTAGCTACAACGA GTCTCCCC	5617
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3305	ACCGCGGC G UGUGGGGA	823	TCCCCACA GGCTAGCTACAACGA GCCGCGGT	5620
3307	CGCGGCGU G UGGGGACA	824	TGTCCCCA GGCTAGCTACAACGA ACGCCGCG	5621
3313	GUGUGGGG A CAUCAUUA	825	TAATGATG GGCTAGCTACAACGA CCCCACAC	5622
3315	GUGGGGAC A UCAUUAUG	826	CATAATGA GGCTAGCTACAACGA GTCCCCAC	5623
3318	GGGCAUUC A UUAUGGGU	827	ACCCATAA GGCTAGCTACAACGA GATGTCCC	5624
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3325	CAUUAUGG G UCUACCUG	829	CAGGTAGA GGCTAGCTACAACGA CCATAATG	5626
3329	AUGGGUCU A CCUGUCUC	830	GAGACAGG GGCTAGCTACAACGA AGACCCAT	5627
3333	GUCUACCU G UCUCGCGC	831	GGCGGAGA GGCTAGCTACAACGA AGGTAGAC	5628
3339	CUGUCUCC G CCCGAAGG	832	CCTTCGGG GGCTAGCTACAACGA GGAGACAG	5629
3357	GGAGGGAG A UACUCCUA	833	TAGGAGTA GGCTAGCTACAACGA CTCCCTCC	5630
3359	AGGGAGAU A CUCCUAGG	834	CCTAGGAG GGCTAGCTACAACGA ATCTCCCT	5631
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3376	ACCAGCCG A CAGUCUUG	837	CAAGACTG GGCTAGCTACAACGA CGGCTGGT	5634
3379	AGCCGACA G UCUUGAGG	838	CCTCAAGA GGCTAGCTACAACGA TGTCCGGT	5635
3389	CUUGAGGG G CAGGGGUG	839	CACCCCTG GGCTAGCTACAACGA CCCTCAAG	5636
3395	GGGCAGGG G UGGCGACU	840	AGTCGCCA GGCTAGCTACAACGA CCCTGCCC	5637
3398	CAGGGGUG G CGACUCCU	841	AGGAGTCG GGCTAGCTACAACGA CACCCCTG	5638
3401	GGGUGGCG A CUCCUCGC	842	GCGAGGAG GGCTAGCTACAACGA CGCCACCC	5639
3408	GACUCCUC G CGCCCAUU	843	AATGGGCG GGCTAGCTACAACGA GAGGAGTC	5640
3410	CUCCUCGC G CCCAUUAC	844	GTAATGGG GGCTAGCTACAACGA GCGAGGAG	5641
3414	UCGCGCCC A UUACGGCC	845	GGCCGTAA GGCTAGCTACAACGA GGGCGCGA	5642
3417	CGCCCAUU A CGGCCUAC	846	GTAGGCCG GGCTAGCTACAACGA AATGGGCG	5643
3420	CCAUUACG G CCUACUCC	847	GGAGTAGG GGCTAGCTACAACGA CGTAATGG	5644
3424	UACGGCCU A CUCCCAAC	848	GTTGGGAG GGCTAGCTACAACGA AGGCCGTA	5645
3431	UACUCCCA A CAGACGCG	849	CGCGTCTG GGCTAGCTACAACGA TGGGAGTA	5646
3435	CCCAACAG A CGCGGGGC	850	GCCCCGCG GGCTAGCTACAACGA CTGTTGGG	5647

3437	CAACAGAC G CGGGGCCU	851	AGGCCCCG GGCTAGCTACAACGA GTCTGTTG	5648
3442	GACGCGGG G CCUGUUG	852	CAAACAGG GGCTAGCTACAACGA CCCGCGTC	5649
3446	CGGGGCCU G UUUGGCU	853	CAGCCAAA GGCTAGCTACAACGA AGGCCCCG	5650
3451	CCUGUUG G CUGCAUUA	854	TAATGCAG GGCTAGCTACAACGA CAAACAGG	5651
3454	GUUUGGCU G CAUUAUCA	855	TGATAATG GGCTAGCTACAACGA AGCCAAAC	5652
3456	UUGGCUGC A UUAUCACC	856	GGTGATAA GGCTAGCTACAACGA GCAGCCAA	5653
3459	GCUGCAU A UCACCAGC	857	GCTGGTGA GGCTAGCTACAACGA AATGCAGC	5654
3462	GCAUUAUC A CCAGCCUC	858	GAGGCTGG GGCTAGCTACAACGA GATAATGC	5655
3466	UAUCACCA G CCUCACGG	859	CCGTGAGG GGCTAGCTACAACGA TGGTGATA	5656
3471	CCAGCCUC A CGGGCCGG	860	CCGGCCCG GGCTAGCTACAACGA GAGGCTGG	5657
3475	CCUCACGG G CCGGGACA	861	TGTCCCGG GGCTAGCTACAACGA CCGTGAGG	5658
3481	GGGCCGGG A CAAGAACC	862	GGTTCCTG GGCTAGCTACAACGA CCCGCCCC	5659
3487	GGACAAGA A CCAAGUCG	863	CGACTTGG GGCTAGCTACAACGA TCTTGTC	5660
3492	AGAACCAA G UCGAGGGG	864	CCCCTCGA GGCTAGCTACAACGA TTGGTTCT	5661
3504	AGGGGGAA G UUCAAGUG	865	CACTTGAA GGCTAGCTACAACGA TTCCCCCT	5662
3510	AAGUCAA G UGUUUC	866	GGAAACCA GGCTAGCTACAACGA TTGAACTT	5663
3513	UUCAAGUG G UUUCCACC	867	GGTGGAAA GGCTAGCTACAACGA CACTTGAA	5664
3519	UGGUUUC A CCGCGACG	868	CGTCGCGG GGCTAGCTACAACGA GGAAACCA	5665
3522	UUUCCACC G CGACGCAG	869	CTGCGTCG GGCTAGCTACAACGA GGTGGAAA	5666
3525	CCACCGCG A CGCAGUCU	870	AGACTGCG GGCTAGCTACAACGA CGCGGTGG	5667
3527	ACCGCGAC G CAGUCUUU	871	AAAGACTG GGCTAGCTACAACGA GTCGCGGT	5668
3530	GCGACGCA G UCUUCCU	872	AGGAAAGA GGCTAGCTACAACGA TGCGTCGC	5669
3540	CUUUCUA G CGACCUGC	873	GCAGGTCG GGCTAGCTACAACGA TAGGAAAG	5670
3543	UCCUAGCG A CCUGCGUC	874	GACGCAGG GGCTAGCTACAACGA CGCTAGGA	5671
3547	AGCGACCU G CGUCAACG	875	CGTTGACG GGCTAGCTACAACGA AGGTCGCT	5672
3549	CGACCUGC G UCAACGGC	876	GCCGTTGA GGCTAGCTACAACGA GCAGGTCG	5673
3553	CUGCGUCA A CGGCGUGU	877	ACACGCCG GGCTAGCTACAACGA TGACGCAG	5674
3556	CGUCAACG G CGUGUGCU	878	AGCACACG GGCTAGCTACAACGA CGTTGACG	5675
3558	UCAACGGC G UGUGCUGG	879	CCAGCACA GGCTAGCTACAACGA GCCGTTGA	5676
3560	AACGGCGU G UGUGGAC	880	GTCCAGCA GGCTAGCTACAACGA ACGCCGTT	5677
3562	CGGCGUGU G CUGGACUG	881	CAGTCCAG GGCTAGCTACAACGA ACACGCCG	5678
3567	UGUGCUGG A CUGUCUAC	882	GTAGACAG GGCTAGCTACAACGA CCAGCACA	5679
3570	GCUGGACU G UCUACCAC	883	GTGGTAGA GGCTAGCTACAACGA AGTCCAGC	5680
3574	GACUGUCU A CCACGGCG	884	CGCCGTGG GGCTAGCTACAACGA AGACAGTC	5681
3577	UGUCUACC A CGGCGCCG	885	CGGCGCCG GGCTAGCTACAACGA GGTAGACA	5682
3580	CUACCACG G CGCGGCU	886	AGCCGGCG GGCTAGCTACAACGA CGTGGTAG	5683
3582	ACCACGGC G CGGCUCA	887	TGAGCCGG GGCTAGCTACAACGA GCCGTGGT	5684
3586	CGGCGCCG G CUCAAAGA	888	TCTTTGAG GGCTAGCTACAACGA CGGCGCCG	5685
3594	GCUCAAAG A CCCUAGCC	889	GGCTAGGG GGCTAGCTACAACGA CTTTGAGC	5686
3600	AGACCCUA G CCGGCCCA	890	TGGGCGCG GGCTAGCTACAACGA TAGGTTCT	5687
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3613	CCCAAAGG G UCCAAUCA	892	TGATTGGA GGCTAGCTACAACGA CCTTTGGG	5689
3618	AGGGUCCA A UCACCCAA	893	TTGGGTGA GGCTAGCTACAACGA TGGACCT	5690
3621	GUCCAAUC A CCCAAUG	894	CATTTGGG GGCTAGCTACAACGA GATTGGAC	5691
3627	UCACCCAA A UGUACACC	895	GGTGTACA GGCTAGCTACAACGA TTGGGTGA	5692
3629	ACCCAAAU G UACACCAA	896	TTGGTGTA GGCTAGCTACAACGA ATTTGGGT	5693
3631	CCAAUGU A CACCAUG	897	CATTGGTG GGCTAGCTACAACGA ACATTTGG	5694
3633	AAAUGUAC A CCAUGUA	898	TACATTGG GGCTAGCTACAACGA GTACATTT	5695
3637	GUACACCA A UGUAGACC	899	GGTCTACA GGCTAGCTACAACGA TGGGTGAC	5696
3639	ACACCAAU G UAGACCAG	900	CTGGTCTA GGCTAGCTACAACGA ATTGGTGT	5697
3643	CAAUGUAG A CCAGGACC	901	GGTCCTGG GGCTAGCTACAACGA CTACATTG	5698
3649	AGACCAGG A CCUCGUCG	902	CGACGAGG GGCTAGCTACAACGA CCTGGTCT	5699
3654	AGGACCUC G UCGGAUGG	903	CCATCCGA GGCTAGCTACAACGA GAGGTCT	5700
3659	CUCGUCGG A UGGCCGGC	904	GCCGGCCA GGCTAGCTACAACGA CCGACGAG	5701
3662	GUCGGAUG G CCGGCGCC	905	GGCGCCGG GGCTAGCTACAACGA CATCCGAC	5702
3666	GAUGGCCG G CGCCCCC	906	GGGGGGCG GGCTAGCTACAACGA CGGCCATC	5703
3668	UGGCCGGC G CCCCCCG	907	CCGGGGGG GGCTAGCTACAACGA GCCGGCCA	5704

3678	CCCCCGGA G CGCGGUCC	908	GGACCGCG GGCTAGCTACAACGA TCCGGGGG	5705
3680	CCCGGAGC G CGGUCCUU	909	AAGGACCG GGCTAGCTACAACGA GTCCTGGG	5706
3683	GGAGCGCG G UCCUUGAC	910	GTCAAGGA GGCTAGCTACAACGA CGCGCTCC	5707
3690	GGUCCUUG A CACCAUGC	911	GCATGGTG GGCTAGCTACAACGA CAAGGACC	5708
3692	UCCUUGAC A CCAUGCAC	912	GTGCATGG GGCTAGCTACAACGA GTCAAGGA	5709
3695	UUGACACC A UGCACUG	913	CAGGTGCA GGCTAGCTACAACGA GGTGTCAA	5710
3697	GACACCAU G CACCUGCG	914	CGCAGGTG GGCTAGCTACAACGA ATGGTGTG	5711
3699	CACCAUGC A CCUGCGGC	915	GCCGCAGG GGCTAGCTACAACGA GCATGGTG	5712
3703	AUGCACCU G CGGCGGCU	916	AGCCGCGG GGCTAGCTACAACGA AGGTGCAT	5713
3706	CACCUGCG G CGGUCGCG	917	CCGAGCCG GGCTAGCTACAACGA CGCAGGTG	5714
3709	CUGCGGCG G CUCGGACC	918	GGTCCGAG GGCTAGCTACAACGA CGCCGCAG	5715
3715	CGGCUCGG A CCUUUACU	919	AGTAAAGG GGCTAGCTACAACGA CCGAGCCG	5716
3721	GGACCUUU A CUUGGUCA	920	TGACCAAG GGCTAGCTACAACGA AAAGGTCC	5717
3726	UUUACUUG G UCACGAGA	921	TCTCGTGA GGCTAGCTACAACGA CAAGTAAA	5718
3729	ACUUGGUC A CGAGACAC	922	GTGTCTCG GGCTAGCTACAACGA GACCAAGT	5719
3734	GUCACGAG A CACGUGA	923	TCAGCGTG GGCTAGCTACAACGA CTCGTGAC	5720
3736	CACGAGAC A CGCUGAUG	924	CATCAGCG GGCTAGCTACAACGA GTCTCGTG	5721
3738	CGAGACAC G CUGAUGUC	925	GACATCAG GGCTAGCTACAACGA GTGTCTCG	5722
3742	ACACGCUG A UGUCAUUC	926	GAATGACA GGCTAGCTACAACGA CAGCGTGT	5723
3744	ACGCUGAU G UCAUCCG	927	CGGAATGA GGCTAGCTACAACGA ATCAGCGT	5724
3747	CUGAUGUC A UUCGGUG	928	CACCGGAA GGCTAGCTACAACGA GACATCAG	5725
3753	UCAUCCG G UGCGCCG	929	CCGCGCA GGCTAGCTACAACGA CGGAATGA	5726
3755	AUCCGGU G CGCGGCG	930	CGCCGCGG GGCTAGCTACAACGA ACCGGAAT	5727
3757	UCCGGUGC G CGGCGGG	931	CCCGCCGG GGCTAGCTACAACGA GCACCGGA	5728
3761	GUGCGCCG G CGGGUGA	932	TCACCCCG GGCTAGCTACAACGA CGGCGCAC	5729
3766	CCGGCGGG G UGACAGCA	933	TGCTGTCA GGCTAGCTACAACGA CCCGCCGG	5730
3769	GCGGGGUG A CAGCAGGG	934	CCCTGTGT GGCTAGCTACAACGA CACCCCGC	5731
3772	GGGUGACA G CAGGGGGA	935	TCCCCTGT GGCTAGCTACAACGA TGTCACCC	5732
3781	CAGGGGGA G CUUACUUA	936	ATAGTAAG GGCTAGCTACAACGA TCCCCTGT	5733
3785	GGGAGCUU A CUAUCCCC	937	GGGGATAG GGCTAGCTACAACGA AAGTCCCC	5734
3788	AGCUUACU A UCCCCCAG	938	CTGGGGGA GGCTAGCTACAACGA AGTAAGCT	5735
3797	UCCCCCAG G CCAUCUC	939	GAGATGGG GGCTAGCTACAACGA CTGGGGGA	5736
3801	CCAGGCCC A UCUCUAC	940	GTAGGAGA GGCTAGCTACAACGA GGGCCTGG	5737
3808	CAUCUCCU A CUUGAAGG	941	CCTTCAAG GGCTAGCTACAACGA AGGAGATG	5738
3817	CUUGAAGG G CUCCUCGG	942	CCGAGGAG GGCTAGCTACAACGA CCTTCAAG	5739
3826	CUCCUCGG G CGGUCCAC	943	GTGGACCG GGCTAGCTACAACGA CCGGAGAG	5740
3829	CUCGGGCG G UCCACUGC	944	GCAGTGGA GGCTAGCTACAACGA CGCCCGAG	5741
3833	GGCGGUCC A CUGCUCUG	945	CAGAGCAG GGCTAGCTACAACGA GGACCGCC	5742
3836	GGUCCACU G CUCUGCCC	946	GGGCAGAG GGCTAGCTACAACGA AGTGGACC	5743
3841	ACUGCUCU G CCCUUCGG	947	CCGAAGGG GGCTAGCTACAACGA AGAGCAGT	5744
3851	CCUUCGGG G CACGUUGU	948	ACAACGTG GGCTAGCTACAACGA CCCGAAGG	5745
3853	UUCGGGGC A CGUUGUGG	949	CCACAACG GGCTAGCTACAACGA GCCCCGAA	5746
3855	CGGGGCAC G UUGUGGGC	950	GCCCACAA GGCTAGCTACAACGA GTGCCCCG	5747
3858	GGCACGUU G UGGGCAUC	951	GATGCCCA GGCTAGCTACAACGA AACGTGCC	5748
3862	CGUUGUGG G CAUCUUCC	952	GGAAGATG GGCTAGCTACAACGA CCACAACG	5749
3864	UUGUGGGC A UCUUCCGG	953	CCGAAGA GGCTAGCTACAACGA GCCACAA	5750
3873	UCUUCGGG G CUGCUGUG	954	CACAGCAG GGCTAGCTACAACGA CCGGAAGA	5751
3876	UCCGGGCU G CUGUGUGC	955	GCACACAG GGCTAGCTACAACGA AGCCGGGA	5752
3879	GGGCGUCU G UGUGCACC	956	GGTGCA CA GGCTAGCTACAACGA AGCAGCCC	5753
3881	GCUGCUGU G UGCACCCG	957	CGGGTGCA GGCTAGCTACAACGA ACAGCAGC	5754
3883	UGCUGUGU G CACCCGGG	958	CCCGGGTG GGCTAGCTACAACGA ACACAGCA	5755
3885	CUGUGUGC A CCCGGGGG	959	CCCCCGGG GGCTAGCTACAACGA GCACACAG	5756
3894	CCCGGGGG G UUGCGAAG	960	CTTCGCAA GGCTAGCTACAACGA CCCCCGGG	5757
3897	GGGGGGUU G CGAAGGCG	961	CGCCTTCG GGCTAGCTACAACGA AACCCCCC	5758
3903	UUGCGAAG G CGGUGGAC	962	GTCCACCG GGCTAGCTACAACGA CTTCGCAA	5759
3906	CGAAGGCG G UGGACUUU	963	AAAGTCCA GGCTAGCTACAACGA CGCCTTCG	5760
3910	GGCGGUGG A CUUUGUAC	964	GTACAAAG GGCTAGCTACAACGA CCACCGCC	5761

3915	UGGACUUU G UACCCGUU	965	AACGGGTA GGCTAGCTACAACGA AAAGTCCA	5762
3917	GACUUUGU A CCCGUUGA	966	TCAACGGG GGCTAGCTACAACGA ACAAAGTC	5763
3921	UUGUACCC G UUGAGUCU	967	AGACTCAA GGCTAGCTACAACGA GGGTACAA	5764
3926	CCCGUUGA G UCUAUGGA	968	TCCATAGA GGCTAGCTACAACGA TCAACGGG	5765
3930	UUGAGUCU A UGGAAACU	969	AGTTTCCA GGCTAGCTACAACGA AGACTCAA	5766
3936	CUAUGGAA A CUACCAUG	970	CATGGTAG GGCTAGCTACAACGA TTCCATAG	5767
3939	UGGAAACU A CCAUGCGG	971	CCGCATGG GGCTAGCTACAACGA AGTTTCCA	5768
3942	AAACUACC A UGCGGUCC	972	GGACCGCA GGCTAGCTACAACGA GGTAGTTT	5769
3944	ACUACCAU G CGGUCCCC	973	GGGGACCG GGCTAGCTACAACGA ATGGTAGT	5770
3947	ACCAUGCG G UCCCCGGU	974	ACCGGGGA GGCTAGCTACAACGA CGCATGGT	5771
3954	GGUCCCCG G UCUUCACG	975	CGTGAAGA GGCTAGCTACAACGA CGGGGACC	5772
3960	CGGUCUUC A CGGACAAC	976	GTTGTCCG GGCTAGCTACAACGA GAAGACCG	5773
3964	CUUCACGG A CAACUCGU	977	ACGAGTTG GGCTAGCTACAACGA CCGTGAAG	5774
3967	CACGGACA A CUCGUCCC	978	GGGACGAG GGCTAGCTACAACGA TGTCCGTG	5775
3971	GACAACUC G UCCCCCCC	979	GGGGGGGA GGCTAGCTACAACGA GAGTTGTC	5776
3981	CCCCCCCA G CCGUACCG	980	CGGTACGG GGCTAGCTACAACGA TGGGGGGG	5777
3984	CCCCAGCC G UACCGCAG	981	CTGCGGTA GGCTAGCTACAACGA GGCTGGGG	5778
3986	CCAGCCGU A CCGCAGAC	982	GTCTGCGG GGCTAGCTACAACGA ACGGCTGG	5779
3989	GCCGUACC G CAGACAUU	983	AATGTCTG GGCTAGCTACAACGA GGTACGGC	5780
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4002	CAUCCAA G UGGCCAC	986	GTGGGCCA GGCTAGCTACAACGA TTGGAATG	5783
4005	UCCAAGUG G CCCACCUA	987	TAGGTGGG GGCTAGCTACAACGA CACTTGGA	5784
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4015	CCACCUAC A CGCUCCA	990	TGGGAGCG GGCTAGCTACAACGA GTAGGTGG	5787
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4023	ACGCUCCC A CUGGCAGC	992	GCTGCCAG GGCTAGCTACAACGA GGGAGCGT	5789
4027	UCCACUG G CAGCGGCA	993	TGCCGCTG GGCTAGCTACAACGA CAGTGGGA	5790
4030	CACUGGCA G CGGCAAGA	994	TCTTGCCG GGCTAGCTACAACGA TGCCAGTG	5791
4033	UGGCAAGG G CAAGAGCA	995	TGCTCTTG GGCTAGCTACAACGA CGCTGCCA	5792
4039	CGGCAAGA G CACUAAGG	996	CCTTAGTG GGCTAGCTACAACGA TCTTGCCG	5793
4041	GCAAGAGC A CUAAGGUA	997	TACCTTAG GGCTAGCTACAACGA GCTCTTGC	5794
4047	GCACUAAG G UACCGGCU	998	AGCCGGTA GGCTAGCTACAACGA CTTAGTGC	5795
4049	ACUAAGGU A CCGGCUGC	999	GCAGCCGG GGCTAGCTACAACGA ACCTTAGT	5796
4053	AGGUACCG G CUGCAUUA	1000	ATATGCAG GGCTAGCTACAACGA CGGTACCT	5797
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4065	CAUAUGCA G CCCAAGGG	1005	CCCTTGGG GGCTAGCTACAACGA TGCATATG	5802
4073	GCCCAAGG G UACAAAGU	1006	ACTTTGTA GGCTAGCTACAACGA CCTTGGGC	5803
4075	CCAAGGGU A CAAAGUGC	1007	GCACTTTG GGCTAGCTACAACGA ACCCTTGG	5804
4080	GGUACAAA G UGCUCGUC	1008	GACGAGCA GGCTAGCTACAACGA TTTGTACC	5805
4082	UACAAAGU G CUCGUCCU	1009	AGGACGAG GGCTAGCTACAACGA ACTTTGTA	5806
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4107	CCGUUACC G CCACCUUA	1015	TAAGGTGG GGCTAGCTACAACGA GGTAACGG	5812
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4125	GGUUUGGG G CGUAUAUG	1018	CATATACG GGCTAGCTACAACGA CCCAAACC	5815
4127	UUUGGGGC G UAUAUGUC	1019	GACATATA GGCTAGCTACAACGA GCCCCAAA	5816
4129	UGGGGCGU A UAUGUCUA	1020	TAGACATA GGCTAGCTACAACGA ACGCCCCA	5817
4131	GGGCGUAU A UGUCUAAG	1021	CTTAGACA GGCTAGCTACAACGA ATACGCCC	5818

4133	GCGUAUUAU G UCUAAGGC	1022	GCCTTAGA GGCTAGCTACAACGA ATATACGC	5819
4140	UGUCUAAG G CACACGGU	1023	ACCGTGTG GGCTAGCTACAACGA CTTAGACA	5820
4142	UCUAAGGC A CACGGUGU	1024	ACACCGTG GGCTAGCTACAACGA GCCTTAGA	5821
4144	UAAGGCAC A CGGUGUCG	1025	CGACACCG GGCTAGCTACAACGA GTGCCTTA	5822
4147	GGCACACG G UGUCGAUC	1026	GATCGACA GGCTAGCTACAACGA CGTGTGCC	5823
4149	CACACGGU G UCGAUCCU	1027	AGGTAGGA GGCTAGCTACAACGA ACCGTGTG	5824
4153	CGGUGUCG A UCCUAACA	1028	TGTTAGGA GGCTAGCTACAACGA CGACACCG	5825
4159	CGAUCCUA A CAUCAGAA	1029	TTCTGATG GGCTAGCTACAACGA TAGGATCG	5826
4161	AUCCUAAC A UCAGAACU	1030	AGTTCTGA GGCTAGCTACAACGA GTTAGGAT	5827
4167	ACAUCAGA A CUGGGGUA	1031	TACCCAG GGCTAGCTACAACGA TCTGATGT	5828
4173	GAACUGGG G UAAGGACC	1032	GGTCCTTA GGCTAGCTACAACGA CCCAGTTC	5829
4179	GGGUAAGG A CCAUCACC	1033	GGTGATGG GGCTAGCTACAACGA CCTTACCC	5830
4182	UAAGGACC A UCACCACG	1034	CGTGGTGA GGCTAGCTACAACGA GGTCCCTTA	5831
4185	GGACCAUC A CCACGGGC	1035	GCCCGTGG GGCTAGCTACAACGA GATGGTCC	5832
4188	CCAUCACC A CGGGCGCC	1036	GGCGCCCG GGCTAGCTACAACGA GGTGATGG	5833
4192	CACCACGG G CGCCCCA	1037	TGGGGGCG GGCTAGCTACAACGA CCGTGGTG	5834
4194	CCACGGGC G CCCCACU	1038	GATGGGGG GGCTAGCTACAACGA GCCCGTGG	5835
4200	GCGCCCCC A UCACGUAC	1039	GTACGTGA GGCTAGCTACAACGA GGGGGCGC	5836
4203	CCCCCAUC A CGUACUCC	1040	GGAGTACG GGCTAGCTACAACGA GATGGGGG	5837
4205	CCCAUCAC G UACUCCAC	1041	GTGGAGTA GGCTAGCTACAACGA GTGATGGG	5838
4207	CAUCACGU A CUCCACCU	1042	AGGTGGAG GGCTAGCTACAACGA ACGTGATG	5839
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4216	CUCCACCU A UGGCAAGU	1044	ACTTGCCA GGCTAGCTACAACGA AGGTGGAG	5841
4219	CACCUAUG G CAAGUUC	1045	GGAACCTG GGCTAGCTACAACGA CATAGGTG	5842
4223	UAUGGCAA G UUCUUGC	1046	GCAAGGAA GGCTAGCTACAACGA TTGCCATA	5843
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4234	CCUUGCCG A CGGUGGUU	1048	AACCACCG GGCTAGCTACAACGA CGGCAAGG	5845
4237	UGCCGACG G UGGUUGCU	1049	AGCAACCA GGCTAGCTACAACGA CGTCGGCA	5846
4240	CGACGGUG G UUGUCUG	1050	CAGAGCAA GGCTAGCTACAACGA CACCGTCG	5847
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4252	CUCUGGGG G CGCUAUG	1052	CATAGGCG GGCTAGCTACAACGA CCCAGAG	5849
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4276	AAUGUGUG A UGAGUGCC	1061	GGCACTCA GGCTAGCTACAACGA CACACATT	5858
4280	UGUGAUGA G UGCCACUC	1062	GAGTGGCA GGCTAGCTACAACGA TCATCACA	5859
4282	UGAUGAGU G CCACUCAA	1063	TTGAGTGG GGCTAGCTACAACGA ACTCATCA	5860
4285	UGAGUGCC A CUCAAUUG	1064	CAATTGAG GGCTAGCTACAACGA GGCATCA	5861
4290	GCCACUCA A UUGACUCG	1065	CGAGTCAA GGCTAGCTACAACGA TGAGTGGC	5862
4294	CUCAAUUG A CUCGACUU	1066	AAGTCGAG GGCTAGCTACAACGA CAATTGAG	5863
4299	UUGACUCG A CUUCCAUU	1067	AATGGAAG GGCTAGCTACAACGA CGAGTCAA	5864
4305	CGACUUC A UUUUGGGC	1068	GCCCAAAA GGCTAGCTACAACGA GGAAGTCG	5865
4312	CAUUUUGG G CAUCGGCA	1069	TGCCGATG GGCTAGCTACAACGA CCAAAATG	5866
4314	UUUUGGGC A UCGGCACA	1070	TGTGCCGA GGCTAGCTACAACGA GCCCAAAA	5867
4318	GGGCAUCG G CACAGUCC	1071	GGACTGTG GGCTAGCTACAACGA CGATGCCC	5868
4320	GCAUCGGC A CAGUCCUG	1072	CAGGACTG GGCTAGCTACAACGA GCCGATGC	5869
4323	UCGGCACA G UCCUGGAC	1073	GTCCAGGA GGCTAGCTACAACGA TGTGCCGA	5870
4330	AGUCCUGG A CCAAGCGG	1074	CCGCTTGG GGCTAGCTACAACGA CCAGGACT	5871
4335	UGGACCAA G CGGAGACG	1075	CGTCTCCG GGCTAGCTACAACGA TTGGTCCA	5872
4341	AAGCGGAG A CGGCUGGA	1076	TCCAGCCG GGCTAGCTACAACGA CTCCGCTT	5873
4344	CGGAGACG G CUGGAGCG	1077	CGTCCAG GGCTAGCTACAACGA CGTCTCCG	5874
4350	CGGCUGGA G CGCGGCUC	1078	GAGCCGCG GGCTAGCTACAACGA TCCAGCCG	5875

4352	GCUGGAGC G CGGCUCGU	1079	ACGAGCCG GGCTAGCTACAACGA GCTCCAGC	5876
4355	GGAGCGCG G CUCGUCGU	1080	ACGACGAG GGCTAGCTACAACGA CGCGCTCC	5877
4359	CGCGGCUC G UCGUGCUC	1081	GAGCACGA GGCTAGCTACAACGA GAGCCGCG	5878
4362	GGCUCGUC G UGCUCGCC	1082	GGCGAGCA GGCTAGCTACAACGA GACGAGCC	5879
4364	CUCGUCGU G CUCGCCAC	1083	GTGGCGAG GGCTAGCTACAACGA ACGACGAG	5880
4368	UCGUGCUC G CCACCGCU	1084	AGCGGTGG GGCTAGCTACAACGA GAGCACGA	5881
4371	UGCUCGCC A CCGCUACG	1085	CGTAGCGG GGCTAGCTACAACGA GGCGAGCA	5882
4374	UCGCCACC G CUACGCCU	1086	AGGCGTAG GGCTAGCTACAACGA GGTGGCGA	5883
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4379	ACCGCUAC G CCUCCGGG	1088	CCCAGGAG GGCTAGCTACAACGA GTAGCGGT	5885
4388	CCUCCGGG A UCGGUCAC	1089	GTGACCGA GGCTAGCTACAACGA CCCGAGG	5886
4392	CGGGAUCG G UCACCGUG	1090	CACGGTGA GGCTAGCTACAACGA CGATCCCG	5887
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4430	AUAGCCUU G UCCAACAC	1100	GTGTTGGA GGCTAGCTACAACGA AAGGCTAT	5897
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4437	UGUCCAAC A CCGGAGAG	1102	CTCTCCGG GGCTAGCTACAACGA GTTGGACA	5899
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4456	CCCCUUCU A UGGCAAAG	1104	CTTTGCCA GGCTAGCTACAACGA AGAAGGGG	5901
4459	CUUCUAUG G CAAAGCCA	1105	TGGCTTTG GGCTAGCTACAACGA CATAGAAG	5902
4464	AUGGCAAA G CCAUCCCC	1106	GGGGATGG GGCTAGCTACAACGA TTTGCCAT	5903
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4513	CUUCUGCC A UUCAAGA	1115	TCCTTGGA GGCTAGCTACAACGA GGCAGAAG	5912
4526	AAGAAGAA A UGUGACGA	1116	TCGTCAAC GGCTAGCTACAACGA TTCTTCTT	5913
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4535	UGUGACGA G CUCGCUGC	1119	GCAGCGAG GGCTAGCTACAACGA TCGTCACA	5916
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4550	GCAAAGCU G UCGGGCCU	1123	AGGCCCCG GGCTAGCTACAACGA AGCTTTGC	5920
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4562	GGCCUCGG A CUUAACGC	1125	GCGTTAAG GGCTAGCTACAACGA CCGAGGCC	5922
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5201	ACACCCCU G CUGUAUAG	1285	CTATACAG GGCTAGCTACAACGA AGGGGTGT	6082
5204	CCCUGCU G UAUAGGCU	1286	AGCCTATA GGCTAGCTACAACGA AGCAGGGG	6083
5206	CCUGCUGU A UAGGCUAG	1287	CTAGCCTA GGCTAGCTACAACGA ACAGCAGG	6084
5210	CUGUAUAG G CUAGGAGC	1288	GCTCCTAG GGCTAGCTACAACGA CTATACAG	6085
5217	GGCUAGGA G CCGUCCAA	1289	TTGGACGG GGCTAGCTACAACGA TCCTAGCC	6086
5220	UAGGAGCC G UCCAAAUA	1290	ATTTTGGG GGCTAGCTACAACGA GGCTCCTA	6087
5227	CGUCCAAA A UGAUGUCA	1291	TGACATCA GGCTAGCTACAACGA TTTGGACG	6088
5230	CCAAAUG A UGUCACCC	1292	GGGTGACA GGCTAGCTACAACGA CATTTTGG	6089
5232	AAAUGAU G UCACCCUC	1293	GAGGGTGA GGCTAGCTACAACGA ATCATTTT	6090
5235	AUGAUGUC A CCCUCACA	1294	TGTGAGGG GGCTAGCTACAACGA GACATCAT	6091
5241	UCACCCUC A CACACCCC	1295	GGGGTGTG GGCTAGCTACAACGA GAGGGTGA	6092
5243	ACCCUCAC A CACCCCAU	1296	ATGGGGTG GGCTAGCTACAACGA GTGAGGGT	6093
5245	CCUCACAC A CCCCAUAA	1297	TTATGGGG GGCTAGCTACAACGA GTGTGAGG	6094
5250	CACACCCC A UAACCAA	1298	TTTGGTTA GGCTAGCTACAACGA GGGGTGTG	6095
5253	ACCCCAUA A CCAAAUAC	1299	GTATTTGG GGCTAGCTACAACGA TATGGGGT	6096
5258	AUAACCAA A UACAUCAU	1300	ATGATGTA GGCTAGCTACAACGA TTGGTTAT	6097
5260	AACCAAU A CAUCAUGA	1301	TCATGATG GGCTAGCTACAACGA ATTTGGTT	6098
5262	CCAAUAC A UCAUGACA	1302	TGTCATGA GGCTAGCTACAACGA GTATTTGG	6099
5265	AAUACAUC A UGACAUGC	1303	GCATGTCA GGCTAGCTACAACGA GATGTATT	6100
5268	ACAUAUG A CAUGCAUG	1304	CATGCATG GGCTAGCTACAACGA CATGATGT	6101
5270	AUCAUGAC A UGCAUGUC	1305	GACATGCA GGCTAGCTACAACGA GTCATGAT	6102
5272	CAUGACAU G CAUGUCGG	1306	CCGACATG GGCTAGCTACAACGA ATGTCATG	6103

5274	UGACAUGC A UGUCGGCU	1307	AGCCGACA GGCTAGCTACAACGA GCATGTCA	6104
5276	ACAUGCAU G UCGGCUA	1308	TCAGCCGA GGCTAGCTACAACGA ATGCATGT	6105
5280	GCAUGUCG G CUGACCUG	1309	CAGGTCAG GGCTAGCTACAACGA CGACATGC	6106
5284	GUCGGCUG A CCUGGAGG	1310	CCTCCAGG GGCTAGCTACAACGA CAGCCGAC	6107
5292	ACCUGGAG G UCGUACC	1311	GGTGACGA GGCTAGCTACAACGA CTCCAGGT	6108
5295	UGGAGGUC G UCACCAGC	1312	GCTGGTGA GGCTAGCTACAACGA GACCTCCA	6109
5298	AGGUCGUC A CCAGCACC	1313	GGTGCTGG GGCTAGCTACAACGA GACGACCT	6110
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5304	UCACCAGC A CCUGGGUG	1315	CACCCAGG GGCTAGCTACAACGA GCTGGTGA	6112
5310	GCACCUGG G UGCUAGUA	1316	TACTAGCA GGCTAGCTACAACGA CCAGGTGC	6113
5312	ACCUGGGU G CUAGUAGG	1317	CCTACTAG GGCTAGCTACAACGA ACCCAGGT	6114
5316	GGGUGCUA G UAGGUGGC	1318	GCCACCTA GGCTAGCTACAACGA TAGCACCC	6115
5320	GCUAGUAG G UGGCGUCC	1319	GGACGCCA GGCTAGCTACAACGA CTACTAGC	6116
5323	AGUAGGUG G CGUCCUGG	1320	CCAGGACG GGCTAGCTACAACGA CACCTACT	6117
5325	UAGGUGGC G UCCUGGCA	1321	TGCCAGGA GGCTAGCTACAACGA GCCACCTA	6118
5331	GCGUCCUG G CAGCUCUG	1322	CAGAGCTG GGCTAGCTACAACGA CAGGACGC	6119
5334	UCCUGGCA G CUCUGACC	1323	GGTCAGAG GGCTAGCTACAACGA TGCCAGGA	6120
5340	CAGCUCUG A CCGCGUAU	1324	ATACGCGG GGCTAGCTACAACGA CAGAGCTG	6121
5343	CUCUGACC G CGUAUUGC	1325	GCAATACG GGCTAGCTACAACGA GGTCAGAG	6122
5345	CUGACCGC G UAUUGCCU	1326	AGGCAATA GGCTAGCTACAACGA GCGGTCAG	6123
5347	GACCGCGU A UUGCCUGA	1327	TCAGGCAA GGCTAGCTACAACGA ACGCGGTC	6124
5350	CGCGUAU G CCUGACGA	1328	TCGTACAG GGCTAGCTACAACGA AATACGCG	6125
5355	AUUGCCUG A CGACAGGC	1329	GCCTGTCT GGCTAGCTACAACGA CAGGCAAT	6126
5358	GCCUGACG A CAGGCAGC	1330	GCTGCCTG GGCTAGCTACAACGA CGTCAGGC	6127
5362	GACGACAG G CAGCGUGG	1331	CCACGCTG GGCTAGCTACAACGA CTGTCTGC	6128
5365	GACAGGCA G CGUGGUCA	1332	TGACCACG GGCTAGCTACAACGA TGCCTGTC	6129
5367	CAGGCAGC G UGGUCAU	1333	AATGACCA GGCTAGCTACAACGA GCTGCCTG	6130
5370	GCAGCGUG G UCAUUGUG	1334	CACAATGA GGCTAGCTACAACGA CACGCTGC	6131
5373	GCGUGGUC A UUGUGGGC	1335	GCCCACAA GGCTAGCTACAACGA GACCACGC	6132
5376	UGGUCAUU G UGGGCAGA	1336	TCTGCCCA GGCTAGCTACAACGA AATGACCA	6133
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5388	GCAGAAUC A UCUUGUCC	1339	GGACAAGA GGCTAGCTACAACGA GATTCTGC	6136
5393	AUCAUCUU G UCCGGGAA	1340	TTCCCGGA GGCTAGCTACAACGA AAGATGAT	6137
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5406	GGAAGCCG G CUGUUAUC	1342	GATAACAG GGCTAGCTACAACGA CGGCTTCC	6139
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5412	CGGCGUUU A UCCCCGAC	1344	GTGCGGGA GGCTAGCTACAACGA AACAGCCG	6141
5419	UAUCCCCG A CAGGGAGG	1345	CCTCCCTG GGCTAGCTACAACGA CGGGGATA	6142
5427	ACAGGGAG G CUCUCUAC	1346	GTAGAGAG GGCTAGCTACAACGA CTCCCTGT	6143
5434	GGCUCUCU A CCAGGAGU	1347	ACTCCTGG GGCTAGCTACAACGA AGAGAGCC	6144
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5446	GGAGUUCG A UGAGAUGG	1349	CCATCTCA GGCTAGCTACAACGA CGAACTCC	6146
5451	UCGAUGAG A UGGAGGAG	1350	CTCCTCCA GGCTAGCTACAACGA CTCATCGA	6147
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5461	GGAGGAGU G UGCCUCAC	1352	GTGAGGCA GGCTAGCTACAACGA ACTCCTCC	6149
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5468	UGUGCCUC A CACCUCCC	1354	GGGAGGTG GGCTAGCTACAACGA GAGGCACA	6151
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5481	UCCCUUAC A UCGAACAG	1357	CTGTTCGA GGCTAGCTACAACGA GTAAGGGA	6154
5486	UACAUCGA A CAGGGGAU	1358	ATCCCCTG GGCTAGCTACAACGA TCGATGTA	6155
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5495	CAGGGGAU G CAGCUCGC	1360	GCGAGCTG GGCTAGCTACAACGA ATCCCCTG	6157
5498	GGGAUGCA G CUCGCCGA	1361	TCGCGCAG GGCTAGCTACAACGA TGCATCCC	6158
5502	UGCAGCUC G CCGAGCAG	1362	CTGCTCGG GGCTAGCTACAACGA GAGCTGCA	6159
5507	CUCGCCGA G CAGUUCAA	1363	TTGAACTG GGCTAGCTACAACGA TCGGCGAG	6160

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5516	CAGUUCAA G CAGAAGGC	1365	GCCTTCTG GGCTAGCTACAACGA TTGAACTG	6162
5523	AGCAGAA G CGCUCGGA	1366	TCCGAGCG GGCTAGCTACAACGA CTTCTGCT	6163
5525	CAGAAGG G CUCGGAU	1367	AATCCGAG GGCTAGCTACAACGA GCCTTCTG	6164
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5537	GGAUUGCU G CAAACAGC	1370	GCTGTTTG GGCTAGCTACAACGA AGCAATCC	6167
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5544	UGCAAACA G CCACCAAC	1372	GTTGGTGG GGCTAGCTACAACGA TGTTTGCA	6169
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5562	AAGCGGAG G CUGCUGCU	1376	AGCAGCAG GGCTAGCTACAACGA CTCCGCTT	6173
5565	CGGAGGCU G CUGCUCU	1377	GGGAGCAG GGCTAGCTACAACGA AGCCTCCG	6174
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5577	CUCCCGUG G UGGAAUCC	1380	GGATTCCA GGCTAGCTACAACGA CACGGGAG	6177
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5588	GAAUCCAA G UGCGAGC	1382	GCTCGCCA GGCTAGCTACAACGA TTGGATTG	6179
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5624	AAGCACAU G UGGAAUUU	1390	AAATTCCA GGCTAGCTACAACGA ATGTGCTT	6187
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5634	GGAAUUUC A UCAGCGGG	1392	CCCGCTGA GGCTAGCTACAACGA GAAATTCC	6189
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5725	CAUCACCA G CCCGCUCA	1416	TGAGCGGG GGCTAGCTACAACGA TGGTGATG	6213
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5736	CGCUCACC A CCCAAAGC	1419	GCTTTGGG GGCTAGCTACAACGA GGTGAGCG	6216
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5948	GGGGAGAU G CCUUCUAC	1467	GTAAGAGG GGCTAGCTACAACGA ATCTCCCC	6264
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5967	AGGACCUG G UCAACUUA	1470	TAAGTTGA GGCTAGCTACAACGA CAGGTCCT	6267
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6018	UCGGGGUG G UGUGCGCA	1480	TGCGCACA GGCTAGCTACAACGA CACCCCGA	6277
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6022	GGUGUGUG G CGCAGCGA	1482	TCGCTGCG GGCTAGCTACAACGA ACACCACC	6279
6024	UGGUGUGC G CAGCGAUA	1483	TATCGCTG GGCTAGCTACAACGA GCACACCA	6280
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6106	UUCGCGGG G CAACCAUG	1506	CATGGTTG GGCTAGCTACAACGA CCCGCGAA	6303
6109	GCGGGGCA A CCAUGUCU	1507	AGACATGG GGCTAGCTACAACGA TGCCCCGC	6304
6112	GGGCAACC A UGUCUCCC	1508	GGGAGACA GGCTAGCTACAACGA GGTGCCCC	6305
6114	GCAACCAU G UCUCCCCC	1509	GGGGGAGA GGCTAGCTACAACGA ATGGTTGC	6306
6123	UCUCCCCC A CGCACUAU	1510	ATAGTGCG GGCTAGCTACAACGA GGGGGAGA	6307
6125	UCCCCCAC G CACUAUGU	1511	ACATAGTG GGCTAGCTACAACGA GTGGGGGA	6308
6127	CCCCACGC A CUAUGUGC	1512	GCACATAG GGCTAGCTACAACGA GCGTGGGG	6309
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6132	CGCACUAU G UGCCUGAG	1514	CTCAGGCA GGCTAGCTACAACGA ATAGTGCG	6311
6134	CACUAUGU G CCUGAGAG	1515	CTCTCAGG GGCTAGCTACAACGA ACATAGTG	6312
6142	GCCUGAGA G CGACGCAG	1516	CTGCGTCG GGCTAGCTACAACGA TCTCAGGC	6313
6145	UGAGAGCG A CGCAGCGG	1517	CCGCTGCG GGCTAGCTACAACGA CGCTCTCA	6314
6147	AGAGCGAC G CAGCGGCG	1518	CGCCGCTG GGCTAGCTACAACGA GTCGCTCT	6315
6150	GCGACGCA G CGGCGCGC	1519	GCGGCGCG GGCTAGCTACAACGA TGCGTTCG	6316
6153	ACGCAGCG G CGCGCGUC	1520	GACGCGCG GGCTAGCTACAACGA CGCTGCGT	6317
6155	GCAGCGGC G CGCGUCAC	1521	GTGACGCG GGCTAGCTACAACGA GCCGCTGC	6318
6157	AGCGGCGC G CGUCACAC	1522	GTGTGACG GGCTAGCTACAACGA GCGCCGCT	6319
6159	CGGCGCGC G UCACACAA	1523	TTGTGTGA GGCTAGCTACAACGA GCGCGCCG	6320
6162	CGCGCGUC A CACAAUUC	1524	GATTGTGT GGCTAGCTACAACGA GACGCGCG	6321
6164	CGCGUCAC A CAAAUCCU	1525	AGGATTTG GGCTAGCTACAACGA GTGACGCG	6322
6168	UCACACAA A UCCUCUCC	1526	GGAGAGGA GGCTAGCTACAACGA TTGTGTGA	6323
6178	CCUCUCCA G CCUCACCA	1527	TGGTGAGG GGCTAGCTACAACGA TGGAGAGG	6324
6183	CCAGCCUC A CCAUCACU	1528	AGTGATGG GGCTAGCTACAACGA GAGGCTGG	6325
6186	GCCUCACC A UCACUCAG	1529	CTGAGTGA GGCTAGCTACAACGA GGTGAGGC	6326
6189	UCACCAUC A CUCAGCUG	1530	CAGCTGAG GGCTAGCTACAACGA GATGGTGA	6327
6194	AUCACUCA G CUGCUGAG	1531	CTCAGCAG GGCTAGCTACAACGA TGAGTGAT	6328
6197	ACUCAGCU G CUGAGGAG	1532	CTCCTCAG GGCTAGCTACAACGA AGCTGAGT	6329
6206	CUGAGGAG G CUCCAUCA	1533	TGATGGAG GGCTAGCTACAACGA CTCCTCAG	6330
6211	GAGGCUCC A UCAGUGGA	1534	TCCACTGA GGCTAGCTACAACGA GGAGCCTC	6331

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6219	AUCAGUGG A UCAAUGAG	1536	CTCATTGA GGCTAGCTACAACGA CCACTGAT	6333
6223	GUGGAUCA A UGAGGACU	1537	AGTCCTCA GGCTAGCTACAACGA TGATCCAC	6334
6229	CAAUGAGG A CUGCUCCA	1538	TGGAGCAG GGCTAGCTACAACGA CCTCATTG	6335
6232	UGAGGACU G UCCACGC	1539	GCGTGGAG GGCTAGCTACAACGA AGTCCTCA	6336
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6239	UGCUCAC G CCAUGUUC	1541	GAACATGG GGCTAGCTACAACGA GTGGAGCA	6338
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6244	CACGCCAU G UUCCGGCU	1543	AGCCGGAA GGCTAGCTACAACGA ATGGCGTG	6340
6250	AUGUCCG G CUCGUGGC	1544	GCCACGAG GGCTAGCTACAACGA CGGAACAT	6341
6254	UCCGGCUC G UGGCUAAG	1545	CTTAGCCA GGCTAGCTACAACGA GAGCCGGA	6342
6257	GGCUCGUG G CUAAGGGA	1546	TCCCTTAG GGCTAGCTACAACGA CACGAGCC	6343
6265	GCUAAGGG A UGUUUGG	1547	CCCAAACA GGCTAGCTACAACGA CCCTTAGC	6344
6267	UAAGGGAU G UUUGGGAC	1548	GTCCCAAA GGCTAGCTACAACGA ATCCCTTA	6345
6274	UGUUUGG A CUGGAUUA	1549	ATATCCAG GGCTAGCTACAACGA CCCAAACA	6346
6279	GGGACUGG A UAUGCACG	1550	CGTGCATA GGCTAGCTACAACGA CCAGTCCC	6347
6281	GACUGGAU A UGCACGGU	1551	ACCGTGCA GGCTAGCTACAACGA ATCCAGTC	6348
6283	CUGGAUUA G CACGGUGU	1552	ACACCGTG GGCTAGCTACAACGA ATATCCAG	6349
6285	GGAUAUGC A CGGUGUUG	1553	CAACACCG GGCTAGCTACAACGA GCATATCC	6350
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6306	ACUUCAAG A CCUGGCUU	1558	AAGCCAGG GGCTAGCTACAACGA CTTGAAGT	6355
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6323	CAGUCCAA G CUCCUGCC	1561	GGCAGGAG GGCTAGCTACAACGA TTGGACTG	6358
6329	AAGCUCCU G CCGCGGUU	1562	AACCGCGG GGCTAGCTACAACGA AGGAGCTT	6359
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6345	UGCCGGGA G UCCUUUC	1566	GAAAGGGA GGCTAGCTACAACGA TCCCGGCA	6363
6359	UUCUUCUC A UGCAACG	1567	CGTTGGCA GGCTAGCTACAACGA GAGAAGAA	6364
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6367	AUGCCAAC G UGGGUACA	1570	TGTACCCA GGCTAGCTACAACGA GTTGGCAT	6367
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6373	ACGUGGGU A CAGGGGGG	1572	CCCCCTG GGCTAGCTACAACGA ACCCACGT	6369
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6386	GGGUCUG G CGGGGAGA	1574	TCTCCCGG GGCTAGCTACAACGA CAGACCCC	6371
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6421	CUGCCCAU G CGGAGCGC	1584	GCGTCCG GGCTAGCTACAACGA ATGGGCAG	6381
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6435	CGCAGAU A CUGGACAU	1588	ATGTCCAG GGCTAGCTACAACGA GATCTGCG	6385
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6442	CACUGGAC A UGUCAAGA	1590	TCTTGACA GGCTAGCTACAACGA GTCCAGTG	6387
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7003	AGACUUUG A CCUCAUCG	1726	CGATGAGG GGCTAGCTACAACGA CAAAGTCT	6523
7008	UUGACCUC A UCGAGGCC	1727	GGCCTCGA GGCTAGCTACAACGA GAGGTCAA	6524
7014	UCAUCGAG G CCAACCUC	1728	GAGGTTGG GGCTAGCTACAACGA CTCGATGA	6525
7018	CGAGGCCA A CCUCCUGU	1729	ACAGGAGG GGCTAGCTACAACGA TGGCCTCG	6526
7025	AACCUCU G UGGCGGCA	1730	TGCCGCCA GGCTAGCTACAACGA AGGAGGTT	6527
7028	CUCCUGUG G CGGCAGGA	1731	TCCTGCCG GGCTAGCTACAACGA CACAGGAG	6528
7031	CUGUGGCG G CAGGAGAU	1732	ATCTCCTG GGCTAGCTACAACGA CGCCACAG	6529
7038	GGCAGGAG A UGGGCGGU	1733	ACCGCCCA GGCTAGCTACAACGA CTCCTGCC	6530
7042	GGAGAUGG G CGGUAACA	1734	TGTTACCG GGCTAGCTACAACGA CCATCTCC	6531
7045	GAUGGGCG G UAACAUA	1735	TGATGTTA GGCTAGCTACAACGA CGCCCATC	6532
7048	GGGCGGUA A CAUCACUC	1736	GAGTGATG GGCTAGCTACAACGA TACCGCCC	6533
7050	GCGGUAAC A UCACUCGC	1737	GCGAGTGA GGCTAGCTACAACGA GTTACCGC	6534
7053	GUAACAUC A CUCGCGUG	1738	CACGCGAG GGCTAGCTACAACGA GATGTTAC	6535
7057	CAUCACUC G CGUGGAGU	1739	ACTCCACG GGCTAGCTACAACGA GAGTGATG	6536
7059	UCACUCGC G UGGAGUCA	1740	TGACTCCA GGCTAGCTACAACGA GCGAGTGA	6537
7064	CGCGUGGA G UCAGAGAA	1741	TTCTCTGA GGCTAGCTACAACGA TCCACGCG	6538
7072	GUCAGAGA A UAAGGUAG	1742	CTACCTTA GGCTAGCTACAACGA TCTCTGAC	6539
7077	AGAAUAAG G UAGUUACC	1743	GGTAACTA GGCTAGCTACAACGA CTTATTCT	6540
7080	AUAAGGUA G UUAACCUUG	1744	CAGGGTAA GGCTAGCTACAACGA TACCTTAT	6541
7083	AGGUAGUU A CCCUGGAC	1745	GTCCAGGG GGCTAGCTACAACGA AACTACCT	6542
7090	UACCCUGG A CUCUUUUG	1746	CAAAAGAG GGCTAGCTACAACGA CCAGGGTA	6543
7099	CUCUUUUG A CCCGCUUC	1747	GAAGCGGG GGCTAGCTACAACGA CAAAAGAG	6544
7103	UUUGACCC G CUUCGAGC	1748	GCTCGAAG GGCTAGCTACAACGA GGGTCAA	6545
7110	CGCUUCGA G CGGAGGAG	1749	CTCTCCG GGCTAGCTACAACGA TCGAAGCG	6546
7120	GGAGGAGG A UGAGAGAG	1750	CTCTCTCA GGCTAGCTACAACGA CCTCTCTC	6547
7131	AGAGAGAG G UGUCCAUA	1751	AATGGACA GGCTAGCTACAACGA CTCTCTCT	6548
7133	AGAGAGGU G UCCAUAUC	1752	GGAATGGA GGCTAGCTACAACGA ACCTCTCT	6549
7137	AGGUGUCC A UUCCGGCG	1753	CGCCGGAA GGCTAGCTACAACGA GGACACCT	6550
7143	CCAUAUCC G CGGAGAUC	1754	GATCTCCG GGCTAGCTACAACGA CGGAATGG	6551
7149	CGGCGGAG A UCCUGCGG	1755	CCGCAGGA GGCTAGCTACAACGA CTCCGCCG	6552
7154	GAGAUCCU G CGGAAUUC	1756	GATTTCGG GGCTAGCTACAACGA AGGATCTC	6553
7160	CUGCGGAA A UCCAAGAA	1757	TTCTTGGA GGCTAGCTACAACGA TTCCGCAG	6554
7169	UCCAAGAA G UUUCUUC	1758	GAAGGAAA GGCTAGCTACAACGA TTCTTGGA	6555
7179	UUCCUUCA G CGUUACCC	1759	GGGTAACG GGCTAGCTACAACGA TGAAGGAA	6556
7181	CCUUCAGC G UUACCCAUA	1760	ATGGGTAA GGCTAGCTACAACGA GCTGAAGG	6557
7184	UCAGCGUU A CCCAUAUG	1761	CATATGGG GGCTAGCTACAACGA AACGCTGA	6558
7188	CGUUAACC A UAUGGGCA	1762	TGCCATA GGCTAGCTACAACGA GGGTAACG	6559

7190	UUACCCAU A UGGGCACG	1763	CGTGCCCA GGCTAGCTACAACGA ATGGGTAA	6560
7194	CCAUAUGG G CACGCCCG	1764	CGGGCGTG GGCTAGCTACAACGA CCATATGG	6561
7196	AUAUGGGC A CGCCCGGA	1765	TCCGGGCG GGCTAGCTACAACGA GCCCATAT	6562
7198	AUGGGCAC G CCCGGAUU	1766	AATCCGGG GGCTAGCTACAACGA GTGCCCAT	6563
7204	ACGCCCGG A UUAACAAC	1767	GGTTGTAA GGCTAGCTACAACGA CCGGGCGT	6564
7207	CCCGGAUU A CAACCCUC	1768	GAGGGTTG GGCTAGCTACAACGA AATCCGGG	6565
7210	GGAUUACA A CCCUCCAC	1769	GTGGAGGG GGCTAGCTACAACGA TGTAATCC	6566
7217	AACCCUCC A CUACUAGA	1770	TCTAGTAG GGCTAGCTACAACGA GGAGGGTT	6567
7220	CCUCCACU A CUAGAGCC	1771	GGCTCTAG GGCTAGCTACAACGA AGTGGAGG	6568
7226	CUACUAGA G CCCUGGAA	1772	TTCCAGGG GGCTAGCTACAACGA TCTAGTAG	6569
7237	CUGGAAAG A CCCAGACU	1773	AGTCTGGG GGCTAGCTACAACGA CTTTCCAG	6570
7243	AGACCCAG A CUACGUCC	1774	GGACGTAG GGCTAGCTACAACGA CTGGGTCT	6571
7246	CCCAGACU A CGUCCUC	1775	GAGGGACG GGCTAGCTACAACGA AGTCTGGG	6572
7248	CAGACUAC G UCCUCCG	1776	CGGAGGGA GGCTAGCTACAACGA GTAGTCTG	6573
7257	UCCUCCG G UGUACAC	1777	GTGTACCA GGCTAGCTACAACGA CGGAGGGA	6574
7260	CUCCGGUG G UACACGGG	1778	CCCCTGTA GGCTAGCTACAACGA CACCGGAG	6575
7262	CCGGUGGU A CACGGGUG	1779	CACCCGTG GGCTAGCTACAACGA ACCACCGG	6576
7264	GGUGGUAC A CGGGUGCC	1780	GGCACCCG GGCTAGCTACAACGA GTACCACC	6577
7268	GUACACGG G UGCCAUU	1781	AATGGGCA GGCTAGCTACAACGA CCGTGTAC	6578
7270	ACACGGGU G CCCAUUGC	1782	GCAATGGG GGCTAGCTACAACGA ACCCGTGT	6579
7274	GGUGGCC A UUGCCACC	1783	GGTGGCAA GGCTAGCTACAACGA GGGCACCC	6580
7277	UGCCCAU G CCACCUGC	1784	GCAGGTGG GGCTAGCTACAACGA AATGGGCA	6581
7280	CCAUUGCC A CCUGCCAA	1785	TTGGCAGG GGCTAGCTACAACGA GGCAATGG	6582
7284	UGCCACCU G CCAAGGCC	1786	GGCCTTGG GGCTAGCTACAACGA AGGTGGCA	6583
7290	CUGCCAAG G CCCCUCCA	1787	TGGAGGGG GGCTAGCTACAACGA CTTGGCAG	6584
7299	CCCUCCA A UACCACCU	1788	AGGTGGTA GGCTAGCTACAACGA TGGAGGGG	6585
7301	CCUCCAAU A CCACCUC	1789	GGAGGTGG GGCTAGCTACAACGA ATTGGAGG	6586
7304	CCAUAACC A CCUCCACG	1790	CGTGGAGG GGCTAGCTACAACGA GGTATTGG	6587
7310	CCACCUC A CGGAGGAA	1791	TTCTCCG GGCTAGCTACAACGA GGAGGTGG	6588
7323	GGAAGAGG A CGGUUGUU	1792	AACAACCG GGCTAGCTACAACGA CCTCTTCC	6589
7326	AGAGGACG G UGUUCUG	1793	CAGAACAA GGCTAGCTACAACGA CGTCTCT	6590
7329	GGACGGUU G UUCUGACA	1794	TGTAGAAA GGCTAGCTACAACGA AACCCTCC	6591
7335	UUGUUCUG A CAGAGUCC	1795	GGACTCTG GGCTAGCTACAACGA CAGAACAA	6592
7340	CUGACAGA G UCCACCGU	1796	ACGCTGGA GGCTAGCTACAACGA TCTGTCAG	6593
7344	CAGAGUCC A CCGUGUCU	1797	AGACACGG GGCTAGCTACAACGA GGACTCTG	6594
7347	AGUCCACC G UGUUCUCU	1798	AGAAGACA GGCTAGCTACAACGA GGTGGACT	6595
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7356	UGUCUUCU G CCUUGGCG	1800	CGCCAAGG GGCTAGCTACAACGA AGAAGACA	6597
7362	CUGCCUUG G CGGAGCUC	1801	GAGCTCCG GGCTAGCTACAACGA CAAGGCAG	6598
7367	UUGGCGGA G CUCGCCAC	1802	GTGGCGAG GGCTAGCTACAACGA TCCGCCAA	6599
7371	CGGAGCUC G CCACAAAG	1803	CTTTGTGG GGCTAGCTACAACGA GAGCTCCG	6600
7374	AGCUCGCC A CAAAGACC	1804	GGTCTTTG GGCTAGCTACAACGA GGCGAGCT	6601
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7387	GACCUUCG G CAGCUCUG	1806	CAGAGCTG GGCTAGCTACAACGA CGAAGGTC	6603
7390	CUUCGGCA G CUCUGAAU	1807	ATTCAGAG GGCTAGCTACAACGA TGCCGAAG	6604
7397	AGCUCUGA A UCAUCGGC	1808	GCCGATGA GGCTAGCTACAACGA TCAGAGCT	6605
7400	UCUGAAUC A UCGGCCGC	1809	GCGGCCGA GGCTAGCTACAACGA GATTCAGA	6606
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7407	CAUCGGCC G CUGAUAGA	1811	TCTATCAG GGCTAGCTACAACGA GGCCGATG	6608
7411	GGCCGCUG A UAGAGGUA	1812	TACCTCTA GGCTAGCTACAACGA CAGCGGCC	6609
7417	UGAUAGAG G UACGGCAA	1813	TTGCCGTA GGCTAGCTACAACGA CTCTATCA	6610
7419	AUAGAGGU A CGGCAACC	1814	GGTTGCCG GGCTAGCTACAACGA ACCTCTAT	6611
7422	GAGGUACG G CAACCGCC	1815	GGCGGTTG GGCTAGCTACAACGA CGTACCTC	6612
7425	GUAGGGCA A CCGCCCCC	1816	GGGGGCGG GGCTAGCTACAACGA TGCCGTAC	6613
7428	CGGCAACC G CCCCCCCC	1817	GGGGGGGG GGCTAGCTACAACGA GGTGCGCG	6614
7438	CCCCCCCC A CCAGACCU	1818	AGGTCTGG GGCTAGCTACAACGA CGGGGGGG	6615
7443	CCGACCAG A CCUCCAAU	1819	ATTGGAGG GGCTAGCTACAACGA CTGGTCGG	6616

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7453	CUCCAAUG A CGGUGACG	1821	CGTCACCG GGCTAGCTACAACGA CATTGGAG	6618
7456	CAAUGACG G UGACGCAG	1822	CTGCGTCA GGCTAGCTACAACGA CGTCATTG	6619
7459	UGACGGUG A CGCAGGAU	1823	ATCCTGCG GGCTAGCTACAACGA CACCGTCA	6620
7461	ACGGUGAC G CAGGAUCC	1824	GGATCCTG GGCTAGCTACAACGA GTCACCGT	6621
7466	GACGCAGG A UCCGACGU	1825	ACGTCGGA GGCTAGCTACAACGA CCTGCGTC	6622
7471	AGGAUCCG A CGUUGAGU	1826	ACTCAACG GGCTAGCTACAACGA CGGATCCT	6623
7473	GAUCCGAC G UUGAGUCG	1827	CGACTCAA GGCTAGCTACAACGA GTCGGATC	6624
7478	GACGUUGA G UCGUACUC	1828	GAGTACGA GGCTAGCTACAACGA TCAACGTC	6625
7481	GUUGAGUC G UACUCCUC	1829	GAGGAGTA GGCTAGCTACAACGA GACTCAAC	6626
7483	UGAGUCGU A CUCCUCUA	1830	TAGAGGAG GGCTAGCTACAACGA ACGACTCA	6627
7491	ACUCCUCU A UGCCCCCC	1831	GGGGGGCA GGCTAGCTACAACGA AGAGGAGT	6628
7493	UCCUCUAU G CCCCCCU	1832	AGGGGGGG GGCTAGCTACAACGA ATAGAGGA	6629
7511	GAGGGGGA G CCGGGGGA	1833	TCCCCCGG GGCTAGCTACAACGA TCCCCCTC	6630
7519	GCCGGGGG A UCCCGAUC	1834	GATCGGGA GGCTAGCTACAACGA CCCCCGGC	6631
7525	GGAUCCCG A UCUCAGCG	1835	CGCTGAGA GGCTAGCTACAACGA CGGGATCC	6632
7531	CGAUCUCA G CGACGGGU	1836	ACCCGTCG GGCTAGCTACAACGA TGAGATCG	6633
7534	UCUCAGCG A CGGGUCUU	1837	AAGACCCG GGCTAGCTACAACGA CGCTGAGA	6634
7538	AGCGACGG G UCUUGGUC	1838	GACCAAGA GGCTAGCTACAACGA CCGTCGCT	6635
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7551	GGUCUACC G UGAGCGAA	1841	TTCGCTCA GGCTAGCTACAACGA GGTAGACC	6638
7555	UACCGUGA G CGAAGAGG	1842	CCTCTTCG GGCTAGCTACAACGA TCACGGTA	6639
7563	GCGAAGAG G CUGGCGAG	1843	CTCGCCAG GGCTAGCTACAACGA CTCTTCGC	6640
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7573	UGGCGAGG A UGUCGUCU	1845	AGACGACA GGCTAGCTACAACGA CCTCGCCA	6642
7575	GCGAGGAU G UCGUCUGC	1846	GCAGACGA GGCTAGCTACAACGA ATCCTCGC	6643
7578	AGGAUGUC G UCUGCUGC	1847	GCAGCAGA GGCTAGCTACAACGA GACATCCT	6644
7582	UGUCGUCU G CUGCUCGA	1848	TCGAGCAG GGCTAGCTACAACGA AGACGACA	6645
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7592	UGCUCGAU G UCCUACAC	1851	GTGTAGGA GGCTAGCTACAACGA ATCGAGCA	6648
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7609	AUGGACGG G CGCCUGA	1856	TCAGGGCG GGCTAGCTACAACGA CCGTCCAT	6653
7611	GGACGGGC G CCCUGAUC	1857	GATCAGGG GGCTAGCTACAACGA GCCCGTCC	6654
7617	GCGCCUG A UCACGCCA	1858	TGGCGTGA GGCTAGCTACAACGA CAGGGCGC	6655
7620	CCCUGAUC A CGCCAUGC	1859	GCATGGCG GGCTAGCTACAACGA GATCAGGG	6656
7622	CUGAUCAC G CCAUGCGC	1860	GCGCATGG GGCTAGCTACAACGA GTGATCAG	6657
7625	AUCACGCC A UGCGCUGC	1861	GCAGCGCA GGCTAGCTACAACGA GCGGTGAT	6658
7627	CACGCCAU G CGCUGCGG	1862	CCGACGCG GGCTAGCTACAACGA ATGGCGTG	6659
7629	CGCCAUGC G CUGCGGAG	1863	CTCCGCAG GGCTAGCTACAACGA GCATGGCG	6660
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7642	GGAGGAAA G CAAGUUGC	1865	GCAACTTG GGCTAGCTACAACGA TTTCTCTC	6662
7646	GAAAGCAA G UUGCCCAU	1866	ATGGGCAA GGCTAGCTACAACGA TTGCTTTC	6663
7649	AGCAAGUU G CCCAUCAA	1867	TTGATGGG GGCTAGCTACAACGA AACTTGCT	6664
7653	AGUUGCCC A UCAACGCG	1868	CGCGTTGA GGCTAGCTACAACGA GGGCAACT	6665
7657	GCCCAUCA A CGCGUUGA	1869	TCAACGCG GGCTAGCTACAACGA TGATGGGC	6666
7659	CCAUCAAC G CGUUGAGC	1870	GCTCAACG GGCTAGCTACAACGA GTTGATGG	6667
7661	AUCAACGC G UUGAGCAA	1871	TTGCTCAA GGCTAGCTACAACGA GCGTTGAT	6668
7666	CGCGUUGA G CAACUCUU	1872	AAGAGTTG GGCTAGCTACAACGA TCAACGCG	6669
7669	GUUGAGCA A CUCUUUGC	1873	GCAAAGAG GGCTAGCTACAACGA TGCTCAAC	6670
7676	AACUCUUU G CUGCGUCA	1874	TGACGCAG GGCTAGCTACAACGA AAAGAGTT	6671
7679	UCUUUGCU G CGUCACCA	1875	TGGTGACG GGCTAGCTACAACGA AGCAAAGA	6672
7681	UUUGCUGC G UCACCACA	1876	TGTTGTGA GGCTAGCTACAACGA GCAGCAAA	6673

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7687	GCGUCACC A CAACAUGG	1878	CCATGTTG GGCTAGCTACAACGA GGTGACGC	6675
7690	UCACCACA A CAUGGUCU	1879	AGACCATG GGCTAGCTACAACGA TGTGGTGA	6676
7692	ACCACAAC A UGGUCUAC	1880	GTAGACCA GGCTAGCTACAACGA GTTGTGGT	6677
7695	ACAACAUG G UCUACGCU	1881	AGCGTAGA GGCTAGCTACAACGA CATGTTGT	6678
7699	CAUGGUCU A CGCUACAA	1882	TTGTAGCG GGCTAGCTACAACGA AGACCATG	6679
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7707	ACGCUACA A CAUCUCGC	1885	GCGAGATG GGCTAGCTACAACGA TGTAGCGT	6682
7709	GCUACAAC A UCUCGCAG	1886	CTGCGAGA GGCTAGCTACAACGA GTTGTAGC	6683
7714	AACAUCUC G CAGCGCAA	1887	TTGCGCTG GGCTAGCTACAACGA GAGATGTT	6684
7717	AUCUCGCA G CGCAAGCC	1888	GGCTTTCG GGCTAGCTACAACGA TGCGAGAT	6685
7719	CUCGCAGC G CAAGCCAG	1889	CTGGCTTG GGCTAGCTACAACGA GCTGCGAG	6686
7723	CAGCGCAA G CCAGCGGC	1890	GCCGCTGG GGCTAGCTACAACGA TTGCGCTG	6687
7727	GCAAGCCA G CGGCAGAA	1891	TTCTGCCG GGCTAGCTACAACGA TGGCTTGC	6688
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7743	AGAAGGUC A CCUUGAC	1894	GTCAAAGG GGCTAGCTACAACGA GACCTTCT	6691
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7754	UUUGACAG A CUGCAAGU	1896	ACTTGCGG GGCTAGCTACAACGA CTGTCAA	6693
7757	GACAGACU G CAAGUCCU	1897	AGGACTTG GGCTAGCTACAACGA AGTCTGTC	6694
7761	GACUGCAA G UCCUGGAC	1898	GTCCAGGA GGCTAGCTACAACGA TTGCAGTC	6695
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7787	CGGGACGU G CUCAAGGA	1905	TCCTTGAG GGCTAGCTACAACGA ACGTCCCG	6702
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7815	AGGCGUCC A CAGUUAAG	1910	CTTAACTG GGCTAGCTACAACGA GGACGCCT	6707
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7824	CAGUUAAG G CUAAACUU	1912	AAGTTTAG GGCTAGCTACAACGA CTTAACTG	6709
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7839	UUCUAUCC G UAGAGGAA	1915	TTCTCTTA GGCTAGCTACAACGA GGATAGAA	6712
7848	UAGAGGAA G CCUGCAGA	1916	TCTGCAGG GGCTAGCTACAACGA TTCTCTTA	6713
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7856	GCCUGCAG A CUGACGCC	1918	GGCGTCAG GGCTAGCTACAACGA CTGCAGGC	6715
7860	GCAGACUG A CGCCCCCA	1919	TGGGGGCG GGCTAGCTACAACGA CAGTCTGC	6716
7862	AGACUGAC G CCCCCACA	1920	TGTGGGGG GGCTAGCTACAACGA GTCAGTCT	6717
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7870	GCCCCCAC A UUCGGCCA	1922	TGGCCGAA GGCTAGCTACAACGA GTGGGGGC	6719
7875	CACAUUCG G CCAGGUCC	1923	GGACCTGG GGCTAGCTACAACGA CGAATGTG	6720
7880	UCGGCCAG G UCCAAAUU	1924	AATTTGGA GGCTAGCTACAACGA CTGGCCGA	6721
7886	AGGUCCAA A UUUGGUUA	1925	TAACCAA GGCTAGCTACAACGA TTGGACCT	6722
7891	CAAUUUG G UUAUGGGG	1926	CCCATAA GGCTAGCTACAACGA CAAATTTG	6723
7894	AUUUGGUU A UGGGGCAA	1927	TTGCCCCA GGCTAGCTACAACGA AACCNAAT	6724
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7906	GGCAAAGG A CGUCCGGA	1929	TCCGGACG GGCTAGCTACAACGA CCTTTGCC	6726
7908	CAAAGGAC G UCCGGAAC	1930	GTTCGGGA GGCTAGCTACAACGA GTCCTTTG	6727
7915	CGUCCGGA A CCUAUCCA	1931	TGGATAGG GGCTAGCTACAACGA TCCGGACG	6728
7919	CGGAACCU A UCCAGCGG	1932	CCGTGGA GGCTAGCTACAACGA AGGTTCCG	6729
7924	CCUAUCCA G CGGGGCCG	1933	CGGCCCGG GGCTAGCTACAACGA TGGATAGG	6730

8183	CCUGGGCA G CGGGUUGA	1991	TCAACCCG GGCTAGCTACAACGA TGCCCAGG	6788
8187	GGCAGCGG G UUGAGUUC	1992	GAACTCAA GGCTAGCTACAACGA CCGCTGCC	6789
8192	CGGGUUGA G UUCCUGGU	1993	ACCAGGAA GGCTAGCTACAACGA TCAACCCG	6790
8199	AGUUCCUG G UGAAUGCC	1994	GGCATTCA GGCTAGCTACAACGA CAGGAACT	6791
8203	CCUGGUGA A UGCCUGGA	1995	TCCAGGCA GGCTAGCTACAACGA TCACCAGG	6792
8205	UGGUGAAU G CCUGGAAA	1996	TTTCCAGG GGCTAGCTACAACGA ATTACCA	6793
8213	GCCUGGAA A UCAAAGAA	1997	TTCTTTGA GGCTAGCTACAACGA TTCCAGGC	6794
8222	UCAAAGAA A UGCCCUAU	1998	ATAGGGCA GGCTAGCTACAACGA TTCTTTGA	6795
8224	AAAGAAAU G CCCUAUGG	1999	CCATAGGG GGCTAGCTACAACGA ATTTCTTT	6796
8229	AAUGCCCU A UGGGCUUU	2000	AAAGCCCA GGCTAGCTACAACGA AGGGCATT	6797
8233	CCCUAUGG G CUUUGCAU	2001	ATGCAAAG GGCTAGCTACAACGA CCATAGGG	6798
8238	UGGGCUUU G CAUAUGAC	2002	GTCATATG GGCTAGCTACAACGA AAAGCCCA	6799
8240	GGCUUUGC A UAUGACAC	2003	GTGTCATA GGCTAGCTACAACGA GCAAAGCC	6800
8242	CUUUGCAU A UGACACCC	2004	GGGTGTCA GGCTAGCTACAACGA ATGCAAAG	6801
8245	UGCAUAUG A CACCCGCU	2005	AGCGGGTG GGCTAGCTACAACGA CATATGCA	6802
8247	CAUAUGAC A CCCGUGU	2006	ACAGCGGG GGCTAGCTACAACGA GTCATATG	6803
8251	UGACACCC G CUGUUUCG	2007	CGAAACAG GGCTAGCTACAACGA GGGTGTCA	6804
8254	CACCCGCU G UUUCGACU	2008	AGTCGAAA GGCTAGCTACAACGA AGCGGGTG	6805
8260	CUGUUUCG A CUCAACAG	2009	CTGTTGAG GGCTAGCTACAACGA CGAAACAG	6806
8265	UCGACUCA A CAGUCACC	2010	GGTGACTG GGCTAGCTACAACGA TGAGTCGA	6807
8268	ACUCAACA G UCACCGAG	2011	CTCGGTGA GGCTAGCTACAACGA TGTTGAGT	6808
8271	CAACAGUC A CCGAGAGU	2012	ACTCTCGG GGCTAGCTACAACGA GACTGTTG	6809
8278	CACCGAGA G UGACAUCC	2013	GGATGTCA GGCTAGCTACAACGA TCTCGGTG	6810
8281	CGAGAGUG A CAUCCGUG	2014	CACGGATG GGCTAGCTACAACGA CACTCTCG	6811
8283	AGAGUGAC A UCCGUGUC	2015	GACACGGA GGCTAGCTACAACGA GTCACTCT	6812
8287	UGACAUCC G UGUCGAGG	2016	CCTCGACA GGCTAGCTACAACGA GGATGTCA	6813
8289	ACAUCCGU G UCGAGGAG	2017	CTCCTCGA GGCTAGCTACAACGA ACGGATGT	6814
8297	GUCGAGGA G UCAAUUUA	2018	TAAATTGA GGCTAGCTACAACGA TCCTCGAC	6815
8301	AGGAGUCA A UUUACCAA	2019	TTGGTAAA GGCTAGCTACAACGA TGACTCCT	6816
8305	GUCAAUUU A CCAAUGUU	2020	AACATTGG GGCTAGCTACAACGA AAATTGAC	6817
8309	AUUUACCA A UGUUGUGA	2021	TCACAACA GGCTAGCTACAACGA TGGTAAAT	6818
8311	UUACCAAU G UUGUGACU	2022	AGTCACAA GGCTAGCTACAACGA ATTGGTAA	6819
8314	CCAAUGUU G UGACUUGG	2023	CCAAGTCA GGCTAGCTACAACGA AACATTGG	6820
8317	AUGUUGUG A CUUGGCCC	2024	GGGCCAAG GGCTAGCTACAACGA CACAACAT	6821
8322	GUGACUUG G CCCCCGAA	2025	TTCCGGGG GGCTAGCTACAACGA CAAGTCAC	6822
8331	CCCCCGAA G CCAGACAG	2026	CTGTCTGG GGCTAGCTACAACGA TTCGGGGG	6823
8336	GAAGCCAG A CAGGCCAU	2027	ATGGCCTG GGCTAGCTACAACGA CTGGCTTC	6824
8340	CCAGACAG G CCAUAAGG	2028	CCTTATGG GGCTAGCTACAACGA CTGTCTGG	6825
8343	GACAGGCC A UAAGGUCG	2029	CGACCTTA GGCTAGCTACAACGA GGCCTGTC	6826
8348	GCCAUAA G UCGCUCAC	2030	GTGAGCGA GGCTAGCTACAACGA CTTATGGC	6827
8351	AUAAGGUC G CUCACAGA	2031	TCTGTGAG GGCTAGCTACAACGA GACCTTAT	6828
8355	GGUCGCUC A CAGAGCGG	2032	CCGCTCTG GGCTAGCTACAACGA GAGCGACC	6829
8360	CUCACAGA G CGGCUUUA	2033	TAAAGCCG GGCTAGCTACAACGA TCTGTGAG	6830
8363	ACAGAGCG G CUUUAUUA	2034	ATATAAAG GGCTAGCTACAACGA CGCTCTGT	6831
8368	GCGGCUUU A UAUCGGGG	2035	CCCCGATA GGCTAGCTACAACGA AAAGCCGC	6832
8370	GGCUUUAU A UCGGGGGU	2036	ACCCCGCA GGCTAGCTACAACGA ATAAAGCC	6833
8377	UAUCGGGG G UCCUCUGA	2037	TCAGAGGA GGCTAGCTACAACGA CCCCATA	6834
8385	GUCCUCUG A CUAAUUCA	2038	TGAATTAG GGCTAGCTACAACGA CAGAGGAC	6835
8389	UCUGACUA A UUCAAAAG	2039	CTTTTGAA GGCTAGCTACAACGA TAGTCAGA	6836
8399	UCAAAAGG G CAGAACUG	2040	CAGTTCTG GGCTAGCTACAACGA CCTTTTGA	6837
8404	AGGGCAGA A CUGCGGUU	2041	AACCGCAG GGCTAGCTACAACGA TCTGCCCT	6838
8407	GCAGAACU G CGGUUAUC	2042	GATAACCG GGCTAGCTACAACGA AGTTCTGC	6839
8410	GAACUCG G UUAUCGCC	2043	GGCGATAA GGCTAGCTACAACGA CGCAGTTC	6840
8413	CUGCGGUU A UCGCCGGU	2044	ACCGGCGA GGCTAGCTACAACGA AACCGCAG	6841
8416	CGGUUAUC G CCGGUGCC	2045	GGCACCGG GGCTAGCTACAACGA GATAACCG	6842
8420	UAUCGCCG G UGCCGCGC	2046	GCGCGGCA GGCTAGCTACAACGA CGGCGATA	6843
8422	UCGCCGGU G CCGCGCGA	2047	TCGCGCGG GGCTAGCTACAACGA ACCGGCGA	6844

8425	CCGGUGCC G CGCGAGCG	2048	CGCTCGCG GGCTAGCTACAACGA GGCACCGG	6845
8427	GGUGCCGC G CGAGCGGC	2049	GCCGCTCG GGCTAGCTACAACGA GCGGCACC	6846
8431	CCGCGCGA G CGGCGUGC	2050	GCACGCCG GGCTAGCTACAACGA TCGCGCGG	6847
8434	CGCGAGCG G CGUGCUGA	2051	TCAGCACG GGCTAGCTACAACGA CGCTCGCG	6848
8436	CGAGCGGC G UGCUGACG	2052	CGTCAGCA GGCTAGCTACAACGA GCCGCTCG	6849
8438	AGCGGCGU G CUGACGAC	2053	GTCGTCAG GGCTAGCTACAACGA ACGCCGCT	6850
8442	GCGUGCUG A CGACCAGC	2054	GCTGGTCG GGCTAGCTACAACGA CAGCACGC	6851
8445	UGCUGACG A CCAGCUGU	2055	ACAGCTGG GGCTAGCTACAACGA CGTCAGCA	6852
8449	GACGACCA G CUGUGGUA	2056	TACCACAG GGCTAGCTACAACGA TGGTCGTC	6853
8452	GACCAGCU G UGGUAAUA	2057	TATTACCA GGCTAGCTACAACGA AGCTGGTC	6854
8455	CAGCUGUG G UAAUACCC	2058	GGGTATTA GGCTAGCTACAACGA CACAGCTG	6855
8458	CUGUGGUA A UACCCUCA	2059	TGAGGGTA GGCTAGCTACAACGA TACCACAG	6856
8460	GUGGUAAU A CCCUCACA	2060	TGTGAGGG GGCTAGCTACAACGA ATTACCAC	6857
8466	AUACCCUC A CAUGUAC	2061	GTAACATG GGCTAGCTACAACGA GAGGGTAT	6858
8468	ACCCUCAC A UGUUACU	2062	AAGTAACA GGCTAGCTACAACGA GTGAGGGT	6859
8470	CCUCACAU G UUAUUGA	2063	TCAAGTAA GGCTAGCTACAACGA ATGTGAGG	6860
8473	CACAUGUU A CUUGAAAG	2064	CTTTCAAG GGCTAGCTACAACGA AACATGTG	6861
8481	ACUUGAAA G CCUCUGCG	2065	CGCAGAGG GGCTAGCTACAACGA TTTCAAGT	6862
8487	AAGCCUCU G CGGCCUGU	2066	ACAGGCCG GGCTAGCTACAACGA AGAGGCTT	6863
8490	CCUCUGCG G CCUGUCGA	2067	TCGACAGG GGCTAGCTACAACGA CGCAGAGG	6864
8494	UGCGGCCU G UCGAGCUG	2068	CAGCTCGA GGCTAGCTACAACGA AGGCCGCA	6865
8499	CCUGUCGA G CUGCGAAG	2069	CTTCGCAG GGCTAGCTACAACGA TCGACAGG	6866
8502	GUCGAGCU G CGAAGCUC	2070	GAGCTTCG GGCTAGCTACAACGA AGCTCGAC	6867
8507	GCUGCGAA G CUCCAGGA	2071	TCCTGGAG GGCTAGCTACAACGA TTCGCAGC	6868
8515	GCUCCAGG A CUGCACGA	2072	TCGTGCAG GGCTAGCTACAACGA CCTGGAGC	6869
8518	CCAGGACU G CACGAUGC	2073	GCATCGTG GGCTAGCTACAACGA AGTCCTGG	6870
8520	AGGACUGC A CGAUGCUC	2074	GAGCATCG GGCTAGCTACAACGA GCAGTCCT	6871
8523	ACUGCACG A UGCUCGUG	2075	CACGAGCA GGCTAGCTACAACGA CGTGCAGT	6872
8525	UGCACGAU G CUCGUGUG	2076	CACACGAG GGCTAGCTACAACGA ATCGTGCA	6873
8529	CGAUGCUC G UGUGUGGA	2077	TCCACACA GGCTAGCTACAACGA GAGCATCG	6874
8531	AUGCUCGU G UGUGGAGA	2078	TCTCCACA GGCTAGCTACAACGA ACGAGCAT	6875
8533	GCUCGUGU G UGGAGACG	2079	CGTCTCCA GGCTAGCTACAACGA ACACGAGC	6876
8539	GUGUGGAG A CGACCUGG	2080	CCAGGTCG GGCTAGCTACAACGA CTCCACAC	6877
8542	UGGAGACG A CCUGGUCG	2081	CGACCAGG GGCTAGCTACAACGA CGTCTCCA	6878
8547	ACGACCUG G UCGUUAUC	2082	GATAACGA GGCTAGCTACAACGA CAGGTCGT	6879
8550	ACCUGGUC G UUAUCUGU	2083	ACAGATAA GGCTAGCTACAACGA GACCAGGT	6880
8553	UGGUCGUU A UCUGUGAA	2084	TTCACAGA GGCTAGCTACAACGA AACGACCA	6881
8557	CGUUAUCU G UGAAAGUG	2085	CAC'TTTC GGCTAGCTACAACGA AGATAACG	6882
8563	CUGUGAAA G UGCGGGGA	2086	TCCCCGCA GGCTAGCTACAACGA TTTACACG	6883
8565	GUGAAAGU G CGGGGACC	2087	GGTCCCCG GGCTAGCTACAACGA ACTTTTAC	6884
8571	GUGCGGGG A CCCAAGAG	2088	CTCTTGGG GGCTAGCTACAACGA CCCC GCAC	6885
8581	CCAAGAGG A CGCGCGCA	2089	TCGCCGCG GGCTAGCTACAACGA CCTCTTGG	6886
8583	AAGAGGAC G CGGCGAGC	2090	GCTCGCCG GGCTAGCTACAACGA GTCCTCTT	6887
8586	AGGACGCG G CGAGCCUA	2091	TAGGCTCG GGCTAGCTACAACGA CGCGTCTT	6888
8590	CGCGGCGA G CCUACGAG	2092	CTCGTAGG GGCTAGCTACAACGA TCGCCGCG	6889
8594	GCGAGCCU A CGAGUCUU	2093	AAGACTCG GGCTAGCTACAACGA AGGCTCGC	6890
8598	GCCUACGA G UCUUCACG	2094	CGTGAAGA GGCTAGCTACAACGA TCGTAGGC	6891
8604	GAGUCUUC A CGGAGGCU	2095	AGCCTCCG GGCTAGCTACAACGA GAAGACTC	6892
8610	UCACGGAG G CUAUGACU	2096	AGTCATAG GGCTAGCTACAACGA CTCCGTGA	6893
8613	CGGAGGCU A UGACUAGG	2097	CCTAGTCA GGCTAGCTACAACGA AGCCTCCG	6894
8616	AGGCUAUG A CUAGGUAC	2098	GTACCTAG GGCTAGCTACAACGA CATAGCCT	6895
8621	AUGACUAG G UACUCUGC	2099	GCAGAGTA GGCTAGCTACAACGA CTAGTCAT	6896
8623	GACUAGGU A CUCUGCCC	2100	GGGCAGAG GGCTAGCTACAACGA ACCTAGTC	6897
8628	GGUACUCU G CCCCCCCC	2101	GGGGGGGG GGCTAGCTACAACGA AGAGTACC	6898
8641	CCCCGGGG A CCGCCCCC	2102	GGGGCGGG GGCTAGCTACAACGA CCGGGGGG	6899
8645	GGGGACCC G CCCAACC	2103	GGTTGGGG GGCTAGCTACAACGA GGGTCCCC	6900
8651	CCGCCCCA A CCGGAUA	2104	TATTCGGG GGCTAGCTACAACGA TGGGGCGG	6901

8657	CAACCGGA A UACGACUU	2105	AAGTCGTA GGCTAGCTACAACGA TCCGGTTG	6902
8659	ACCGGAU A CGACUUGG	2106	CCAAGTCG GGCTAGCTACAACGA ATCCGGT	6903
8662	GGAAUACG A CUUGGAGU	2107	ACTCCAAG GGCTAGCTACAACGA CGTATTCC	6904
8669	GACUUGGA G UUGAUAA	2108	GTTATCAA GGCTAGCTACAACGA TCCAAGTC	6905
8673	UGGAGUUG A UAACAUA	2109	TGATGTTA GGCTAGCTACAACGA CAACTCCA	6906
8676	AGUUGAUA A CAUAGUC	2110	GCATGATG GGCTAGCTACAACGA TATCAACT	6907
8678	UUGAUAA A UCAUGCUC	2111	GAGCATGA GGCTAGCTACAACGA GTTATCAA	6908
8681	AUAACAUC A UGCUCCUC	2112	GAGGAGCA GGCTAGCTACAACGA GATGTTAT	6909
8683	AACAUCAU G CUCCUCCA	2113	TGGAGGAG GGCTAGCTACAACGA ATGATGTT	6910
8692	CUCCUCCA A CGUAUCAG	2114	CTGATACG GGCTAGCTACAACGA TGGAGGAG	6911
8694	CCUCCAAC G UAUCAGUU	2115	AACTGATA GGCTAGCTACAACGA GTTGGAGG	6912
8696	UCCAACGU A UCAGUUGC	2116	GCAACTGA GGCTAGCTACAACGA ACGTTGGA	6913
8700	ACGUAUCA G UUGCACAC	2117	GTGTGCAA GGCTAGCTACAACGA TGATACGT	6914
8703	UAUCAGUU G CACACGAU	2118	ATCGTGTG GGCTAGCTACAACGA AACTGATA	6915
8705	UCAGUUGC A CACGAUGC	2119	GCATCGTG GGCTAGCTACAACGA GCAACTGA	6916
8707	AGUUGCAC A CGAUGCAU	2120	ATGCATCG GGCTAGCTACAACGA GTGCAACT	6917
8710	UGCACACG A UGCAUCUG	2121	CAGATGCA GGCTAGCTACAACGA CGTGTGCA	6918
8712	CACACGAU G CAUCUGGC	2122	GCCAGATG GGCTAGCTACAACGA ATCGTGTG	6919
8714	CACGAUGC A UCUGGCAA	2123	TTGCCAGA GGCTAGCTACAACGA GCATCGTG	6920
8719	UGCAUCUG G CAAAAGGG	2124	CCCTTTTG GGCTAGCTACAACGA CAGATGCA	6921
8727	GCAAAAGG G UGUACUAC	2125	GTAGTACA GGCTAGCTACAACGA CCTTTTGC	6922
8729	AAAAGGGU G UACUACCU	2126	AGGTAGTA GGCTAGCTACAACGA ACCCTTTT	6923
8731	AAGGGUGU A CUACCUCA	2127	TGAGGTAG GGCTAGCTACAACGA ACACCCTT	6924
8734	GGUGUACU A CCUCACCC	2128	GGGTGAGG GGCTAGCTACAACGA AGTACACC	6925
8739	ACUACCUC A CCCGUGAC	2129	GTCACGGG GGCTAGCTACAACGA GAGGTAGT	6926
8743	CCUCACCC G UGACCCCA	2130	TGGGGTCA GGCTAGCTACAACGA GGGTGAGG	6927
8746	CACCCGUG A CCCCACCA	2131	TGGTGGGG GGCTAGCTACAACGA CACGGGTG	6928
8751	GUGACCCC A CCACCCC	2132	GGGGGTGG GGCTAGCTACAACGA GGGGTCAC	6929
8754	ACCCCAAC A CCCCCCU	2133	AAGGGGGG GGCTAGCTACAACGA GGTGGGGT	6930
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8765	CCCCUUGC G CGGGCUGC	2135	GCAGCCCG GGCTAGCTACAACGA GCAAGGGG	6932
8769	UUGCGCGG G CUGCGUGG	2136	CCACGCAG GGCTAGCTACAACGA CCGCGCAA	6933
8772	CGCGGGCU G CGUGGGAG	2137	CTCCCACG GGCTAGCTACAACGA AGCCCGCG	6934
8774	CGGGCUGC G UGGGAGAC	2138	GTCTCCCA GGCTAGCTACAACGA GCAGCCCG	6935
8781	CGUGGGAG A CAGCUAGA	2139	TCTACTTG GGCTAGCTACAACGA CTCCCACG	6936
8784	GGGAGACA G CUAGAAGC	2140	GCTTCTAG GGCTAGCTACAACGA TGTCTCCC	6937
8791	AGCUAGAA G CACUCCAG	2141	CTGGAGTG GGCTAGCTACAACGA TTCTAGCT	6938
8793	CUAGAAGC A CUCCAGUC	2142	GACTGGAG GGCTAGCTACAACGA GCTTCTAG	6939
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8803	UCCAGUCA A CUCCUGGC	2144	GCCAGGAG GGCTAGCTACAACGA TGACTGGA	6941
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8815	CUGGCUAG G CAACAUA	2146	TGATGTTG GGCTAGCTACAACGA CTAGCCAG	6943
8818	GCUAGGCA A CAUCAUA	2147	TGATGATG GGCTAGCTACAACGA TGCCTAGC	6944
8820	UAGGCAAC A UCAUAUG	2148	CATGATGA GGCTAGCTACAACGA GTTGCCTA	6945
8823	GCAACAUC A UCAUGUUU	2149	AAACATGA GGCTAGCTACAACGA GATGTTGC	6946
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8828	AUCAUCAU G UUUGCACC	2151	GGTGCAA GGCTAGCTACAACGA ATGATGAT	6948
8832	UCAUGUUU G CACCCACU	2152	AGTGGGTG GGCTAGCTACAACGA AAACATGA	6949
8834	AUGUUUGC A CCCACUCU	2153	AGAGTGGG GGCTAGCTACAACGA GCAAACAT	6950
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8856	UAAGGAUG A UUCUGAUG	2158	CATCAGAA GGCTAGCTACAACGA CATCCTTA	6955
8862	UGAUUCUG A UGACUCAC	2159	GTGAGTCA GGCTAGCTACAACGA CAGAATCA	6956
8865	UUCUGAUG A CUCACUUC	2160	GAAGTGAG GGCTAGCTACAACGA CATCAGAA	6957
8869	GAUGACUC A CUUCUUCU	2161	AGAAGAAG GGCTAGCTACAACGA GAGTCATC	6958

8880	UCUUCUCC A UCCUUCUA	2162	TAGAAGGA GGCTAGCTACAACGA GGAGAAGA	6959
8889	UCCUUCUA G CCCAGGAG	2163	CTCCTGGG GGCTAGCTACAACGA TAGAAGGA	6960
8897	GCCCAGGA G CAACUUGA	2164	TCAAGTTG GGCTAGCTACAACGA TCCTGGGC	6961
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8917	AGCCCUAG A CUGCCAGA	2167	TCTGGCAG GGCTAGCTACAACGA CTAGGGCT	6964
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8938	CGGGGCUU G UUAUCUCA	2172	TGGAGTAA GGCTAGCTACAACGA AAGCCCCG	6969
8941	GGCUUGUU A CUCCAUG	2173	CAATGGAG GGCTAGCTACAACGA AACAAGCC	6970
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8954	AUUGAGCC A CUUGACCU	2176	AGGTCAAG GGCTAGCTACAACGA GGCTCAAT	6973
8959	GCCACUUG A CCUACCUC	2177	GAGGTAGG GGCTAGCTACAACGA CAAGTGGC	6974
8963	CUUGACCU A CCUCAGAU	2178	ATCTGAGG GGCTAGCTACAACGA AGGTCAAG	6975
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8973	CUCAGAU A UUCAGCGA	2180	TCGCTGAA GGCTAGCTACAACGA GATCTGAG	6977
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8981	AUUCAGCG A CUCCAUGG	2182	CCATGGAG GGCTAGCTACAACGA CGCTGAAT	6979
8986	GCGACUCC A UGGUCUUA	2183	TAAGACCA GGCTAGCTACAACGA GGAGTCGC	6980
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8997	GUCUUAGC G CAUUUUA	2186	TGAAAATG GGCTAGCTACAACGA GCTAAGAC	6983
8999	CUUAGCGC A UUUUCACU	2187	AGTGAAAA GGCTAGCTACAACGA GCGCTAAG	6984
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9013	ACUCCAUA G UUACUCCC	2190	GGGAGTAA GGCTAGCTACAACGA TATGGAGT	6987
9016	CCAUAAGU A CUCCCAG	2191	CTGGGGAG GGCTAGCTACAACGA AACTATGG	6988
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9042	AUAGGGUG G CAUCAUGC	2196	GCATGATG GGCTAGCTACAACGA CACCTTAT	6993
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9047	GUGGCAUC A UGCCUCAG	2198	CTGAGGCA GGCTAGCTACAACGA GATGCCAC	6995
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9071	GGGUUACC A CCUUGCG	2203	CGCAAGGG GGCTAGCTACAACGA GGTACCCC	7000
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9091	CUGGAGAC A UCGGGCCA	2207	TGGCCCGA GGCTAGCTACAACGA GTCTCCAG	7004
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9109	AAGUGUUC G CGCUAAGC	2211	GCTTAGCG GGCTAGCTACAACGA GAACACTT	7008
9111	GUGUUCG G CUAAGCUA	2212	TAGCTTAG GGCTAGCTACAACGA GCGAACAC	7009
9116	CGCGCUAA G CUACUGUC	2213	GACAGTAG GGCTAGCTACAACGA TTAGCGCG	7010
9119	GCUAAGCU A CUGUCCCA	2214	TGGGACAG GGCTAGCTACAACGA AGCTTAGC	7011
9122	AAGCUACU G UCCAGGG	2215	CCCTGGGA GGCTAGCTACAACGA AGTAGCTT	7012
9138	GGGGGAGG G CCGCCACC	2216	GGTGGCGG GGCTAGCTACAACGA CCTCCCCC	7013
9141	GGAGGGCC G CCACCUGU	2217	ACAGGTGG GGCTAGCTACAACGA GGCCCTCC	7014
9144	GGGCCGCC A CCUGUGGC	2218	GCCACAGG GGCTAGCTACAACGA GGCGCCCC	7015

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9151	CACCUGUG G CAGGUACC	2220	GGTACCTG GGCTAGCTACAACGA CACAGGTG	7017
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9157	UGGCAGGU A CCUCUUA	2222	TGAAGAGG GGCTAGCTACAACGA ACCTGCCA	7019
9166	CCUCUUA A CUGGGCAG	2223	CTGCCCAG GGCTAGCTACAACGA TGAAGAGG	7020
9171	UCAACUGG G CAGUAAAG	2224	CTTTACTG GGCTAGCTACAACGA CCAGTTGA	7021
9174	ACUGGGCA G UAAAGACC	2225	GGTCTTTA GGCTAGCTACAACGA TGCCCAGT	7022
9180	CAGUAAAG A CCAAACUC	2226	GAGTTTGG GGCTAGCTACAACGA CTTTACTG	7023
9185	AAGACCAA A CUCAAACU	2227	AGTTTGGG GGCTAGCTACAACGA TTGGTCTT	7024
9191	AAACUCAA A CUCACUCC	2228	GGAGTGAG GGCTAGCTACAACGA TTGAGTTT	7025
9195	UCAACUC A CUCCAAUC	2229	GATTGGAG GGCTAGCTACAACGA GAGTTTGA	7026
9201	UCACUCCA A UCCCAGCU	2230	AGCTGGGA GGCTAGCTACAACGA TGGAGTGA	7027
9207	CAAUCCCA G CUGCGUCU	2231	AGACGCAG GGCTAGCTACAACGA TGGGATTG	7028
9210	UCCCAGCU G CGUCUCAG	2232	CTGAGACG GGCTAGCTACAACGA AGCTGGGA	7029
9212	CCAGCUGC G UCUCAGUU	2233	AACTGAGA GGCTAGCTACAACGA GCAGCTGG	7030
9218	GCGUCUCA G UUGGACUU	2234	AAGTCCAA GGCTAGCTACAACGA TGAGACGC	7031
9223	UCAGUUGG A CUUGUCCA	2235	TGGACAAG GGCTAGCTACAACGA CCAACTGA	7032
9227	UUGGACUU G UCCAACUG	2236	CAGTTGGA GGCTAGCTACAACGA AAGTCCAA	7033
9232	CUUGUCCA A CUGGUUCG	2237	CGAACCAG GGCTAGCTACAACGA TGGACAAG	7034
9236	UCCAACUG G UUCGUUGC	2238	GCAACGAA GGCTAGCTACAACGA CAGTTGGA	7035
9240	ACUGGUUC G UUGCUGGC	2239	GCCAGCAA GGCTAGCTACAACGA GAACCAGT	7036
9243	GGUUCGUU G CUGGCUAC	2240	GTAGCCAG GGCTAGCTACAACGA AACGAACC	7037
9247	CGUUGCUG G CUACAGCG	2241	CGCTGTAG GGCTAGCTACAACGA CAGCAACG	7038
9250	UGCUGGCU A CAGCGGGG	2242	CCCCGCTG GGCTAGCTACAACGA AGCCAGCA	7039
9253	UGGCUACA G CGGGGGAG	2243	CTCCCCCG GGCTAGCTACAACGA TGTAGCCA	7040
9262	CGGGGGAG A CGUGUAUC	2244	GATACACG GGCTAGCTACAACGA CTCCCCCG	7041
9264	GGGGAGAC G UGUUAUC	2245	GTGATACA GGCTAGCTACAACGA GTCTCCCC	7042
9266	GGAGACGU G UAUCACAG	2246	CTGTGATA GGCTAGCTACAACGA ACGTCTCC	7043
9268	AGACGUGU A UCACAGCC	2247	GGCTGTGA GGCTAGCTACAACGA ACACGTCT	7044
9271	CGUGUAUC A CAGCCUGU	2248	ACAGGCTG GGCTAGCTACAACGA GATACACG	7045
9274	GUAUCACA G CCUGUCUC	2249	GAGACAGG GGCTAGCTACAACGA TGTGATAC	7046
9278	CACACCU G UCUCGUGC	2250	GCACGAGA GGCTAGCTACAACGA AGGCTGTG	7047
9283	CCUGUCUC G UGCCGAC	2251	GTGCGGGA GGCTAGCTACAACGA GAGACAGG	7048
9285	UGUCUCGU G CCCGACCC	2252	GGGTCGGG GGCTAGCTACAACGA ACGAGACA	7049
9290	CGUGCCCG A CCCCGCUG	2253	CAGCGGGG GGCTAGCTACAACGA CGGGCACG	7050
9295	CCGACCCC G CUGGUUCA	2254	TGAACCAG GGCTAGCTACAACGA GGGGTCGG	7051
9299	CCCCGCUG G UUCAUGCU	2255	AGCATGAA GGCTAGCTACAACGA CAGCGGGG	7052
9303	GCUGGUUC A UGUUUGC	2256	GCAAAGCA GGCTAGCTACAACGA GAACCAGC	7053
9305	UGGUUCAU G CUUUGCCU	2257	AGGCAAAG GGCTAGCTACAACGA ATGAACCA	7054
9310	CAUGCUUU G CCUACUCC	2258	GGAGTAGG GGCTAGCTACAACGA AAAGCATG	7055
9314	CUUUGCCU A CUCCUACU	2259	AGTAGGAG GGCTAGCTACAACGA AGGCAAAG	7056
9320	CUACUCCU A CUCUCCGU	2260	ACGGAGAG GGCTAGCTACAACGA AGGAGTAG	7057
9327	UACUCUCC G UAGGGGUA	2261	TACCCCTA GGCTAGCTACAACGA GGAGAGTA	7058
9333	CCGUAGGG G UAGGCAUC	2262	GATGCCTA GGCTAGCTACAACGA CCCTACGG	7059
9337	AGGGGUAG G CAUCUACC	2263	GGTAGATG GGCTAGCTACAACGA CTACCCCT	7060
9339	GGGUAGGC A UCUACCUG	2264	CAGGTAGA GGCTAGCTACAACGA GCCTACCC	7061
9343	AGGCAUCU A CCUGCUC	2265	GGAGCAGG GGCTAGCTACAACGA AGATGCCT	7062
9347	AUCUACCU G CUCCCCAA	2266	TTGGGGAG GGCTAGCTACAACGA AGGTAGAT	7063
9355	GCUCCCCA A CCGAUGAA	2267	TTTCATCGG GGCTAGCTACAACGA TGGGGAGC	7064
9359	CCCAACCG A UGAACAGG	2268	CCTGTTC A GGCTAGCTACAACGA CGGTTGGG	7065
9363	ACCGAUGA A CAGGGAGC	2269	GCTCCCTG GGCTAGCTACAACGA TCATCGGT	7066
9370	AACAGGGA G CUAACAC	2270	GTGTTTAG GGCTAGCTACAACGA TCCCTGTT	7067
9375	GGAGCUAA A CACUCCAG	2271	CTGGAGTG GGCTAGCTACAACGA TTAGCTCC	7068
9377	AGCUAAAC A CUCCAGGC	2272	GCCTGGAG GGCTAGCTACAACGA GTTTAGCT	7069
9384	CACUCCAG G CCAAUAGG	2273	CCTATTGG GGCTAGCTACAACGA CTGGAGTG	7070
9388	CCAGGCCA A UAGGCCAU	2274	ATGGCCTA GGCTAGCTACAACGA TGGCCTGG	7071
9392	GCCAAUAG G CCAUCCCG	2275	CGGGATGG GGCTAGCTACAACGA CTATTGGC	7072

9395	AAUAGGCC A UCCCGUUU	2276	AAACGGGA GGCTAGCTACAACGA GGCCTATT	7073
9400	GCCAUCCC G UUUUUUUU	2277	AAAAAAAA GGCTAGCTACAACGA GGGATGGC	7074

Input Sequence = HPCK1S1. Cut Site = R/Y

Arm Length = 8. Core Sequence = GGCTAGCTACAACGA

HPCK1S1 Hepatitis C virus (strain HCV-1b, clone HCV-K1-S1), complete genome; acc#
gi|1030702|dbj|D50483.1; 9410 nt

Table IV: HCV minus strand DNzyme and Substrate Sequence

Pos	Substrate	SeqID	DNzyme	SeqID
9413	AAAAAAA A CGGAUGG	2278	CCATCCCG GGCTAGCTACAACGA TTTT	7075
9408	AAAACGGG A UGGCUAU	2279	ATAGGCCA GGCTAGCTACAACGA CCCGTTT	7076
9405	ACGGGAUG G CCUAUUGG	2280	CCAATAGG GGCTAGCTACAACGA CATCCCGT	7077
9401	GAUGGCCU A UUGGCCUG	2281	CAGGCCAA GGCTAGCTACAACGA AGGCCATC	7078
9397	GCCUAUUG G CCUGGAGU	2282	ACTCCAGG GGCTAGCTACAACGA CAATAGGC	7079
9390	GGCCUGGA G UGUUAGC	2283	GCTAAACA GGCTAGCTACAACGA TCCAGGCC	7080
9388	CCUGGAGU G UUUAGCUC	2284	GAGCTAAA GGCTAGCTACAACGA ACTCCAGG	7081
9383	AGUGUUUA G CUCCUGU	2285	ACAGGGAG GGCTAGCTACAACGA TAAACACT	7082
9376	AGCUCCCU G UUCAUCGG	2286	CCGATGAA GGCTAGCTACAACGA AGGGAGCT	7083
9372	CCCUGUUC A UCGGUUGG	2287	CCAACCGA GGCTAGCTACAACGA GAACAGGG	7084
9368	GUUCAUCG G UUGGGGAG	2288	CTCCCCAA GGCTAGCTACAACGA CGATGAAC	7085
9360	GUUGGGGA G CAGGUAGA	2289	TCTACCTG GGCTAGCTACAACGA TCCCCAAC	7086
9356	GGGAGCAG G UAGAUGCC	2290	GGCATCTA GGCTAGCTACAACGA CTGCTCCC	7087
9352	GCAGGUAG A UGCCUACC	2291	GGTAGGCA GGCTAGCTACAACGA CTACCTGC	7088
9350	AGGUAGAU G CCUACCCC	2292	GGGGTAGG GGCTAGCTACAACGA ATCTACCT	7089
9346	AGAUGCCU A CCCUACG	2293	CGTAGGGG GGCTAGCTACAACGA AGGCATCT	7090
9340	CUACCCCU A CGGAGAGU	2294	ACTCTCCG GGCTAGCTACAACGA AGGGGTAG	7091
9333	UACGGAGA G UAGGAGUA	2295	TACTCCTA GGCTAGCTACAACGA TCTCCGTA	7092
9327	GAGUAGGA G UAGGCAA	2296	TTTGCTTA GGCTAGCTACAACGA TCCTACTC	7093
9323	AGGAGUAG G CAAAGCAU	2297	ATGCTTTG GGCTAGCTACAACGA CTACTCCT	7094
9318	UAGGCAA G CAUGAAC	2298	GGTTCATG GGCTAGCTACAACGA TTTGCTTA	7095
9316	GGCAAAGC A UGAACAG	2299	CTGGTTCA GGCTAGCTACAACGA GCTTTGCC	7096
9312	AAGCAUGA A CCAGCGGG	2300	CCCCTGG GGCTAGCTACAACGA TCATGCTT	7097
9308	AUGAACCA G CGGGGUCG	2301	CGACCCCG GGCTAGCTACAACGA TGGTTCAT	7098
9303	CCAGCGGG G UCGGGCAC	2302	GTGCCCGA GGCTAGCTACAACGA CCCCTGG	7099
9298	GGGGUCGG G CACGAGAC	2303	GTCTCGTG GGCTAGCTACAACGA CCGACCCC	7100
9296	GGUCGGGC A CGAGACAG	2304	CTGTCTCG GGCTAGCTACAACGA GCCGACC	7101
9291	GGCACGAG A CAGGCUGU	2305	ACAGCCTG GGCTAGCTACAACGA CTGCTGCC	7102
9287	CGAGACAG G CUGUGAUA	2306	TATCACAG GGCTAGCTACAACGA CTGTCTCG	7103
9284	GACAGGCU G UGAUACAC	2307	GTGTATCA GGCTAGCTACAACGA AGCCTGTC	7104
9281	AGGCUGUG A UACACGUC	2308	GACGTGTA GGCTAGCTACAACGA CACAGCCT	7105
9279	GCUGUGAU A CACGUCUC	2309	GAGACGTG GGCTAGCTACAACGA ATCACAGC	7106
9277	UGUGAUAC A CGUCUCCC	2310	GGGAGACG GGCTAGCTACAACGA GTATCACA	7107
9275	UGAUACAC G UCUCUCCC	2311	GGGGGAGA GGCTAGCTACAACGA GTGTATCA	7108
9266	UCUCUCCC G CUGUAGCC	2312	GGCTACAG GGCTAGCTACAACGA GGGGGAGA	7109
9263	CCCCCGCU G UAGCCAGC	2313	GCTGGCTA GGCTAGCTACAACGA AGCGGGGG	7110
9260	CCGCUGUA G CCAGCAAC	2314	GTTGCTGG GGCTAGCTACAACGA TACAGCGG	7111
9256	UGUAGCCA G CAACGAAC	2315	GTTGCTTG GGCTAGCTACAACGA TGGCTACA	7112
9253	AGCCAGCA A CGAACAG	2316	CTGGTTCG GGCTAGCTACAACGA TGCTGGCT	7113
9249	AGCAACGA A CCAGUUGG	2317	CCAACCTG GGCTAGCTACAACGA TCGTGTCT	7114
9245	ACGAACCA G UUGGACAA	2318	TTGTCCAA GGCTAGCTACAACGA TGGTTCGT	7115
9240	CCAGUUGG A CAAGUCCA	2319	TGGACTTG GGCTAGCTACAACGA CCAACTGG	7116
9236	UUGGACAA G UCCAACUG	2320	CAGTTGGA GGCTAGCTACAACGA TTGTCCAA	7117
9231	CAAGUCCA A CUGAGACG	2321	CGTCTCAG GGCTAGCTACAACGA TGGACTTG	7118
9225	CAACUGAG A CGCAGCUG	2322	CAGCTGCG GGCTAGCTACAACGA CTCAGTTG	7119
9223	ACUGAGAC G CAGCUGGG	2323	CCCAGCTG GGCTAGCTACAACGA GTCTCAGT	7120
9220	GAGACGCA G CUGGGAUU	2324	AATCCCAG GGCTAGCTACAACGA TGGCTCTC	7121
9214	CAGCUGGG A UUGGAGUG	2325	CACTCCAA GGCTAGCTACAACGA CCCAGCTG	7122
9208	GGAUUGGA G UGAGUUUG	2326	CAAACTCA GGCTAGCTACAACGA TCAATCC	7123
9204	UGGAGUGA G UUGAGUUU	2327	AACTCAA GGCTAGCTACAACGA TCACTCCA	7124
9198	GAGUUUGA G UUGGUCU	2328	AGACCAA GGCTAGCTACAACGA TCAAACTC	7125
9193	UGAGUUUG G UCUUUACU	2329	AGTAAAGA GGCTAGCTACAACGA CAACTCA	7126

9187	UGGUCUUU A CUGCCCAG	2330	CTGGGCAG GGCTAGCTACAACGA AAAGACCA	7127
9184	UCUUUACU G CCCAGUUG	2331	CAACTGGG GGCTAGCTACAACGA AGTAAAGA	7128
9179	ACUGCCCA G UUGAAGAG	2332	CTCTTCAA GGCTAGCTACAACGA TGGGCAGT	7129
9170	UUGAAGAG G UACCUGCC	2333	GGCAGGTA GGCTAGCTACAACGA CTCTTCAA	7130
9168	GAAGAGGU A CCUGCCAC	2334	GTGGCAGG GGCTAGCTACAACGA ACCTCTTC	7131
9164	AGGUACCU G CCACAGGU	2335	ACCTGTGG GGCTAGCTACAACGA AGGTACCT	7132
9161	UACCUGCC A CAGGUGGC	2336	GCCACCTG GGCTAGCTACAACGA GGCAGGTA	7133
9157	UGCCACAG G UGGCGGCC	2337	GGCCGCCA GGCTAGCTACAACGA CTGTGGCA	7134
9154	CACAGGUG G CGGCCUC	2338	GAGGGCCG GGCTAGCTACAACGA CACCTGTG	7135
9151	AGGUGGCG G CCCUCCCC	2339	GGGGAGGG GGCTAGCTACAACGA GCCACCT	7136
9135	CCCCUGGG A CAGUAGCU	2340	AGCTACTG GGCTAGCTACAACGA CCGGGGG	7137
9132	CUGGGACA G UAGCUUAG	2341	CTAAGCTA GGCTAGCTACAACGA TGTCCCAG	7138
9129	GGACAGUA G CUUAGCGC	2342	GCGCTAAG GGCTAGCTACAACGA TACTGTCC	7139
9124	GUAGCUUA G CGCGAACA	2343	TGTTTCGC GGCTAGCTACAACGA TAAGCTAC	7140
9122	AGCUUAGC G CGAACACU	2344	AGTGTTCG GGCTAGCTACAACGA GCTAAGCT	7141
9118	UAGCGCGA A CACUUCUG	2345	CAGAAGTG GGCTAGCTACAACGA TCGCGCTA	7142
9116	GCGCGAAC A CUUCUGGC	2346	GCCAGAAG GGCTAGCTACAACGA GTTCGCGC	7143
9109	CACUUCUG G CCCGAUGU	2347	ACATCGGG GGCTAGCTACAACGA CAGAAGTG	7144
9104	CUGGCCCC A UGUCUCCA	2348	TGGAGACA GGCTAGCTACAACGA CGGGCCAG	7145
9102	GGCCCGAU G UCUCAGG	2349	CCTGGAGA GGCTAGCTACAACGA ATCGGGCC	7146
9094	GUCUCCAG G UUCGCAAG	2350	CTTGCGAA GGCTAGCTACAACGA CTGGAGAC	7147
9090	CCAGGUUC G CAAGGGUG	2351	CACCCTTG GGCTAGCTACAACGA GAACCTGG	7148
9084	UCGCAAGG G UGGUACCC	2352	GGGTACCA GGCTAGCTACAACGA CCTTGCGA	7149
9081	CAAGGGUG G UACCCCAA	2353	TTGGGGTA GGCTAGCTACAACGA CACCCTTG	7150
9079	AGGGUGGU A CCCCAAGU	2354	ACTTGGGG GGCTAGCTACAACGA ACCACCCT	7151
9072	UACCCCAA G UUUCUGA	2355	TCAGGAAA GGCTAGCTACAACGA TTGGGGTA	7152
9062	UUCUGAG G CAUGAUGC	2356	GCATCATG GGCTAGCTACAACGA CTCAGGAA	7153
9060	CCUGAGGC A UGAUGCCA	2357	TGGCATCA GGCTAGCTACAACGA GCCTCAGG	7154
9057	GAGGCAUG A UGCCACCC	2358	GGGTGGCA GGCTAGCTACAACGA CATGCCTC	7155
9055	GGCAUGAU G CCACCCUA	2359	TAGGGTGG GGCTAGCTACAACGA ATCATGCC	7156
9052	AUGAUGCC A CCCUAUUG	2360	CAATAGGG GGCTAGCTACAACGA GGCATCAT	7157
9047	GCCACCCU A UUGAUUUC	2361	GAAATCAA GGCTAGCTACAACGA AGGGTGGC	7158
9043	CCCUAUUG A UUUCACCU	2362	AGGTGAAA GGCTAGCTACAACGA CAATAGGG	7159
9038	UUGAUUUC A CCUGGGGA	2363	TCCCCAGG GGCTAGCTACAACGA GAAATCAA	7160
9029	CCUGGGGA G UAACUAUG	2364	CATAGTTA GGCTAGCTACAACGA TCCCCAGG	7161
9026	GGGGAGUA A CUAUGGAG	2365	CTCCATAG GGCTAGCTACAACGA TACTCCCC	7162
9023	GAGUAACU A UGGAGUGA	2366	TCACTCCA GGCTAGCTACAACGA AGTTACTC	7163
9018	ACUAUGGA G UGAAAUG	2367	CATTTTCA GGCTAGCTACAACGA TCCATAGT	7164
9012	GAGUGAAA A UGCGCUAA	2368	TTAGCGCA GGCTAGCTACAACGA TTTCACTC	7165
9010	GUGAAAAU G CGCUAAGA	2369	TCTTAGCG GGCTAGCTACAACGA ATTTTCAC	7166
9008	GAAAAUGC G CUAAGACC	2370	GGTCTTAG GGCTAGCTACAACGA GCATTTTC	7167
9002	GCGCUAAG A CCAUGGAG	2371	CTCCATGG GGCTAGCTACAACGA CTTAGCGC	7168
8999	CUAAGACC A UGGAGUCG	2372	CGACTCCA GGCTAGCTACAACGA GGTCTTAG	7169
8994	ACCAUGGA G UCGUGAA	2373	TTCAGCGA GGCTAGCTACAACGA TCCATGGT	7170
8991	AUGGAGUC G CUGAUGA	2374	TCATTGAG GGCTAGCTACAACGA GACTCCAT	7171
8986	GUCGUGA A UGAUCUGA	2375	TCAGATCA GGCTAGCTACAACGA TCAGCGAC	7172
8983	GCUGAAUG A UCUGAGGU	2376	ACCTCAGA GGCTAGCTACAACGA CATTCAGC	7173
8976	GAUCUGAG G UAGGUCAA	2377	TTGACCTA GGCTAGCTACAACGA CTCAGATC	7174
8972	UGAGGUAG G UCAAGUGG	2378	CCACTTGA GGCTAGCTACAACGA CTACCTCA	7175
8967	UAGGUCAA G UGGCUCAA	2379	TTGAGCCA GGCTAGCTACAACGA TTGACCTA	7176
8964	GUCAAGUG G CUCAAUGG	2380	CCATTGAG GGCTAGCTACAACGA CACTTGAC	7177
8959	GUGGCUCA A UGGAGUAA	2381	TTACTCCA GGCTAGCTACAACGA TGAGCCAC	7178
8954	UCAUUGGA G UAACAAGC	2382	GCTTGTTA GGCTAGCTACAACGA TCCATTGA	7179
8951	AUGGAGUA A CAAGCCCC	2383	GGGGCTTG GGCTAGCTACAACGA TACTCCAT	7180
8947	AGUAACAA G CCCCUGAG	2384	CTACGGGG GGCTAGCTACAACGA TTGTTACT	7181
8942	CAAGCCCC G UAGAUCUG	2385	CAGATCTA GGCTAGCTACAACGA GGGGCTTG	7182
8938	CCCCGUAG A UCUGGCAG	2386	CTGCCAGA GGCTAGCTACAACGA CTACGGGG	7183

8933	UAGAUCUG G CAGUCUAG	2387	CTAGACTG GGCTAGCTACAACGA CAGATCTA	7184
8930	AUCUGGCA G UCUAGGGC	2388	GCCCTAGA GGCTAGCTACAACGA TGCCAGAT	7185
8923	AGUCUAGG G CUUUCUCA	2389	TGAGAAAG GGCTAGCTACAACGA CCTAGACT	7186
8913	UUUCUCAA G UUGCUCU	2390	AGGAGCAA GGCTAGCTACAACGA TTGAGAAA	7187
8910	CUCAAGUU G CUCCUGGG	2391	CCCAGGAG GGCTAGCTACAACGA AACTTGAG	7188
8902	GCUCCUGG G CUAGAAGG	2392	CCTTCTAG GGCTAGCTACAACGA CCAGGAGC	7189
8893	CUAGAAGG A UGAGAAG	2393	CTTCTCCA GGCTAGCTACAACGA CCTTCTAG	7190
8882	GAGAAGAA G UGAGUCAU	2394	ATGACTCA GGCTAGCTACAACGA TTCTTCTC	7191
8878	AGAAGUGA G UCAUCAGA	2395	TCTGATGA GGCTAGCTACAACGA TCACTTCT	7192
8875	AGUGAGUC A UCAGAAUC	2396	GATTCTGA GGCTAGCTACAACGA GACTCACT	7193
8869	UCAUCAGA A UCAUCCUU	2397	AAGGATGA GGCTAGCTACAACGA TCTGATGA	7194
8866	UCAGAAUC A UCCUUACC	2398	GGTAAGGA GGCTAGCTACAACGA GATTCTGA	7195
8860	UCAUCCUU A CCCAUAGA	2399	TCTATGGG GGCTAGCTACAACGA AAGGATGA	7196
8856	CCUUACCC A UAGAGUGG	2400	CCACTCTA GGCTAGCTACAACGA GGGTAAGG	7197
8851	CCCAUAGA G UGGGUGCA	2401	TGCACCCA GGCTAGCTACAACGA TCTATGGG	7198
8847	UAGAGUGG G UGCAAACA	2402	TGTTTGCA GGCTAGCTACAACGA CCACTCTA	7199
8845	GAGUGGGU G CAAACAUG	2403	CATGTTTG GGCTAGCTACAACGA ACCCACTC	7200
8841	GGGUGCAA A CAUGAUGA	2404	TCATCATG GGCTAGCTACAACGA TTGCACCC	7201
8839	GUGCAAAC A UGAUGAUG	2405	CATCATCA GGCTAGCTACAACGA GTTTGCAC	7202
8836	CAAACAUG A UGAUGUUG	2406	CAACATCA GGCTAGCTACAACGA CATGTTTG	7203
8833	ACAUGAUG A UGUUGCCU	2407	AGGCAACA GGCTAGCTACAACGA CATCATGT	7204
8831	AUGAUGAU G UUGCCUAG	2408	CTAGGCAA GGCTAGCTACAACGA ATCATCAT	7205
8828	AUGAUGUU G CCUAGCCA	2409	TGGTAGG GGCTAGCTACAACGA AACATCAT	7206
8823	GUUGCCUA G CCAGGAGU	2410	ACTCCTGG GGCTAGCTACAACGA TAGGCAAC	7207
8816	AGCCAGGA G UUGACUGG	2411	CCAGTCAA GGCTAGCTACAACGA TCCTGGCT	7208
8812	AGGAGUUG A CUGGAGUG	2412	CACTCCAG GGCTAGCTACAACGA CAACTCCT	7209
8806	UGACUGGA G UGCUUCUA	2413	TAGAAGCA GGCTAGCTACAACGA TCCAGTCA	7210
8804	ACUGGAGU G CUUCUAGC	2414	GCTAGAAG GGCTAGCTACAACGA ACTCCAGT	7211
8797	UGCUUCUA G CUGUCUCC	2415	GGAGACAG GGCTAGCTACAACGA TAGAAGCA	7212
8794	UUCUAGCU G UCUCCAC	2416	GTGGGAGA GGCTAGCTACAACGA AGCTAGAA	7213
8787	UGUCUCCC A CGCAGCCC	2417	GGGCTGCG GGCTAGCTACAACGA GGGAGACA	7214
8785	UCUCCAC G CAGCCGCG	2418	GCGGGCTG GGCTAGCTACAACGA GTGGGAGA	7215
8782	CCCACGCA G CCCGCGCA	2419	TGCGCGGG GGCTAGCTACAACGA TGCGTGGG	7216
8778	CGCAGCCC G CGCAAGGG	2420	CCCTTGCG GGCTAGCTACAACGA GGGCTGCG	7217
8776	CAGCCGCG G CAAGGGGG	2421	CCCCCTTG GGCTAGCTACAACGA GCGGGCTG	7218
8767	CAAGGGGG G UGGUGGGG	2422	CCCCACCA GGCTAGCTACAACGA CCCCCCTG	7219
8764	GGGGGGUG G UGGGGUCA	2423	TGACCCCA GGCTAGCTACAACGA CACCCCCC	7220
8759	GUGGUGGG G UCACGGGU	2424	ACCCGTGA GGCTAGCTACAACGA CCCACCAC	7221
8756	GUGGGGUC A CGGGUGAG	2425	CTCACCCG GGCTAGCTACAACGA CACCCAC	7222
8752	GGUCACGG G UGAGGUAG	2426	CTACCTCA GGCTAGCTACAACGA CCGTGACC	7223
8747	CGGGUGAG G UAGUACAC	2427	GTGTACTA GGCTAGCTACAACGA CTCACCCG	7224
8744	GUGAGGUA G UACACCU	2428	AGGGTGTA GGCTAGCTACAACGA TACCTCAC	7225
8742	GAGGUAGU A CACCCUU	2429	AAAGGGTG GGCTAGCTACAACGA ACTACCTC	7226
8740	GGUAGUAC A CCCUUUUG	2430	CAAAGGGG GGCTAGCTACAACGA GTACTACC	7227
8732	ACCCUUUU G CCAGAUGC	2431	GCATCTGG GGCTAGCTACAACGA AAAAGGGT	7228
8727	UUUGCCAG A UGCAUCGU	2432	ACGATGCA GGCTAGCTACAACGA CTGGCAAA	7229
8725	UGCCAGAU G CAUCGUGU	2433	ACACGATG GGCTAGCTACAACGA ATCTGGCA	7230
8723	CCAGAUGC A UCGUGUGC	2434	GCACACGA GGCTAGCTACAACGA GCATCTGG	7231
8720	GAUGCAUC G UGUGCAAC	2435	GTTGCACA GGCTAGCTACAACGA GATGCATC	7232
8718	UGCAUCGU G UGCAACUG	2436	CAGTTGCA GGCTAGCTACAACGA ACGATGCA	7233
8716	CAUCGUGU G CAACUGAU	2437	ATCAGTTG GGCTAGCTACAACGA ACACGATG	7234
8713	CGUGUGCA A CUGAUACG	2438	CGTATCAG GGCTAGCTACAACGA TGACACG	7235
8709	UGCAACUG A UACGUUGG	2439	CCAACGTA GGCTAGCTACAACGA CAGTTGCA	7236
8707	CAACUGAU A CGUUGGAG	2440	CTCCAACG GGCTAGCTACAACGA ATCAGTTG	7237
8705	ACUGAUAC G UUGGAGGA	2441	TCCTCAA GGCTAGCTACAACGA GTATCAGT	7238
8696	UUGGAGGA G CAUGAUGU	2442	ACATCATG GGCTAGCTACAACGA TCCTCAA	7239
8694	GGAGGAGC A UGAUGUUA	2443	TAACATCA GGCTAGCTACAACGA GTCCTCC	7240

8691	GGAGCAUG A UGUUAUCA	2444	TGATAACA GGCTAGCTACAACGA CATGCTCC	7241
8689	AGCAUGAU G UUAUCAAC	2445	GTTGATAA GGCTAGCTACAACGA ATCATGCT	7242
8686	AUGAUGUU A UCAACUCC	2446	GGAGTTGA GGCTAGCTACAACGA AACATCAT	7243
8682	UGUUAUCA A CUCCAAGU	2447	ACTTGGAG GGCTAGCTACAACGA TGATAACA	7244
8675	AACUCCAA G UCGUAUUC	2448	GAATACGA GGCTAGCTACAACGA TTGGAGTT	7245
8672	UCCAAGUC G UAUUCCGG	2449	CCGGAATA GGCTAGCTACAACGA GACTTGGA	7246
8670	CAAGUCGU A UUCCGGUU	2450	AACCGGAA GGCTAGCTACAACGA ACGACTTG	7247
8664	GUAUUCCG G UUGGGGCG	2451	CGCCCCAA GGCTAGCTACAACGA CGGAATAC	7248
8658	CGGUUGGG G CGGGUCCC	2452	GGGACCCG GGCTAGCTACAACGA CCCAACCG	7249
8654	UGGGGCGG G UCCCCGGG	2453	CCCGGGGA GGCTAGCTACAACGA CCGCCCCA	7250
8641	CGGGGGGG G CAGAGUAC	2454	GTACTCTG GGCTAGCTACAACGA CCCCCCG	7251
8636	GGGGCAGA G UACCUAGU	2455	ACTAGGTA GGCTAGCTACAACGA TCTGCCCC	7252
8634	GGCAGAGU A CCUAGUCA	2456	TGACTAGG GGCTAGCTACAACGA ACTCTGCC	7253
8629	AGUACCUA G UCAUAGCC	2457	GGCTATGA GGCTAGCTACAACGA TAGGTACT	7254
8626	ACCUAGUC A UAGCCUCC	2458	GGAGGCTA GGCTAGCTACAACGA GACTAGGT	7255
8623	UAGUCAUA G CCUCCGUG	2459	CACGGAGG GGCTAGCTACAACGA TATGACTA	7256
8617	UAGCCUCC G UGAAGACU	2460	AGTCTTCA GGCTAGCTACAACGA GGAGGCTA	7257
8611	CCGUGAAG A CUCGUAGG	2461	CCTACGAG GGCTAGCTACAACGA CTTACACG	7258
8607	GAAGACUC G UAGGCUCG	2462	CGAGCCTA GGCTAGCTACAACGA GAGTCTTC	7259
8603	ACUCGUAG G CUCGCCGC	2463	GCGGCGAG GGCTAGCTACAACGA CTACGAGT	7260
8599	GUAGGCUC G CCGCGUCC	2464	GGACGCGG GGCTAGCTACAACGA GAGCCTAC	7261
8596	GGCUCGCC G CGUCCUCU	2465	AGAGGACG GGCTAGCTACAACGA GGCGAGCC	7262
8594	CUCGCCGC G UCCUCUUG	2466	CAAGAGGA GGCTAGCTACAACGA GCGGCGAG	7263
8584	CCUCUUGG G UCCCCGCA	2467	TGCGGGGA GGCTAGCTACAACGA CCAAGAGG	7264
8578	GGGUCCCC G CACUUUCA	2468	TGAAAGTG GGCTAGCTACAACGA GGGGACCC	7265
8576	GUCCCCGC A CUUUCACA	2469	TGTGAAAG GGCTAGCTACAACGA GCGGGGAC	7266
8570	GCACUUUC A CAGUAUAC	2470	GTTATCTG GGCTAGCTACAACGA GAAAGTGC	7267
8566	UUUCACAG A UAACGACC	2471	GGTCGTTA GGCTAGCTACAACGA CTGTGAAA	7268
8563	CACAGUA A CGACCAGG	2472	CCTGGTCG GGCTAGCTACAACGA TATCTGTG	7269
8560	AGAUAAAG A CCAGGUCG	2473	CGACCTGG GGCTAGCTACAACGA CGTTATCT	7270
8555	ACGACCAG G UCGUCUCC	2474	GGAGACGA GGCTAGCTACAACGA CTGGTCGT	7271
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8546	UCGUCUCC A CACAGAG	2476	CTCGTGTG GGCTAGCTACAACGA GGAGACGA	7273
8544	GUCUCCAC A CACGAGCA	2477	TGCTCGTG GGCTAGCTACAACGA GTGGAGAC	7274
8542	CUCCACAC A CGAGCAUC	2478	GATGCTCG GGCTAGCTACAACGA GTGTGGAG	7275
8538	ACACACGA G CAUCGUGC	2479	GCACGATG GGCTAGCTACAACGA TCGTGTGT	7276
8536	ACACGAGC A UCGUGCAG	2480	CTGCACGA GGCTAGCTACAACGA GTCGTGT	7277
8533	CGAGCAUC G UGCAGUCC	2481	GGACTGCA GGCTAGCTACAACGA GATGCTCG	7278
8531	AGCAUCGU G CAGUCCUG	2482	CAGGACTG GGCTAGCTACAACGA ACGTGTCT	7279
8528	AUCGUGCA G UCCUGGAG	2483	CTCCAGGA GGCTAGCTACAACGA TGCACGAT	7280
8520	GUCCUGGA G CUUCGCAG	2484	CTGCGAAG GGCTAGCTACAACGA TCCAGGAC	7281
8515	GGAGCUUC G CAGCUCGA	2485	TCGAGCTG GGCTAGCTACAACGA GAAGCTCC	7282
8512	GCUUCGCA G CUCGACAG	2486	CTGTGCGG GGCTAGCTACAACGA TGCGAAGC	7283
8507	GCAGCUCG A CAGGCCGC	2487	GCGGCCTG GGCTAGCTACAACGA CGAGCTGC	7284
8503	CUCGACAG G CCGCAGAG	2488	CTCTGCGG GGCTAGCTACAACGA CTGTGCGG	7285
8500	GACAGGCC G CAGAGGCU	2489	AGCCTCTG GGCTAGCTACAACGA GGCCTGTC	7286
8494	CCGCAGAG G CUUUCAAG	2490	CTTGAAAG GGCTAGCTACAACGA CTCTGCGG	7287
8486	GCUUUCAA G UAACAUGU	2491	ACATGTTA GGCTAGCTACAACGA TTGAAAGC	7288
8483	UUCAAGUA A CAUGUGAG	2492	CTCACATG GGCTAGCTACAACGA TACTTGAA	7289
8481	CAAGUAAC A UGUGAGGG	2493	CCCTCACA GGCTAGCTACAACGA GTTACTTG	7290
8479	AGUAACAU G UGAGGGUA	2494	TACCCTCA GGCTAGCTACAACGA ATGTACT	7291
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8471	GUGAGGUU A UUACCACA	2496	TGTGGTAA GGCTAGCTACAACGA ACCCTCAC	7293
8468	AGGGUAUU A CCACAGCU	2497	AGCTGTGG GGCTAGCTACAACGA AATACCCT	7294
8465	GUUUUACC A CAGCUGGU	2498	ACCAGCTG GGCTAGCTACAACGA GGTAATAC	7295
8462	UUACCACA G CUGGUCGU	2499	ACGACCAG GGCTAGCTACAACGA TGTGGTAA	7296
8458	CACAGCUG G UCGUCAGC	2500	GCTGACGA GGCTAGCTACAACGA CAGCTGTG	7297

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8451	GGUCGUCA G CACGCCGC	2502	GCGGCGTG GGCTAGCTACAACGA TGACGACC	7299
8449	UCGUCAGC A CGCCGCUC	2503	GAGCGGCG GGCTAGCTACAACGA GCTGACGA	7300
8447	GUCAGCAC G CCGCUCGC	2504	GCGAGCGG GGCTAGCTACAACGA GTGCTGAC	7301
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8435	CUCGCGCG G CACCGGCG	2508	CGCCGGTG GGCTAGCTACAACGA CGCGCGAG	7305
8433	CGCGCGGC A CCGGCGAU	2509	ATCGCCGG GGCTAGCTACAACGA GCCGCGCG	7306
8429	CGGCACCG G CGAUAAACC	2510	GGTTATCG GGCTAGCTACAACGA CGGTGCCG	7307
8426	CACCGGCG A UAACCGCA	2511	TGCGGTTA GGCTAGCTACAACGA CGCCGGTG	7308
8423	CGGCGAUA A CCGCAGUU	2512	AACTGCCG GGCTAGCTACAACGA TATCGCCG	7309
8420	CGAUAAACC G CAGUUCUG	2513	CAGAACTG GGCTAGCTACAACGA GGTTATCG	7310
8417	UAACCGCA G UUCUGCCC	2514	GGGCAGAA GGCTAGCTACAACGA TGCGGTTA	7311
8412	GCAGUUCU G CCCUUUUG	2515	CAAAAGGG GGCTAGCTACAACGA AGAACTGC	7312
8402	CCUUUUGA A UUAGUCAG	2516	CTGACTAA GGCTAGCTACAACGA TCAAAAGG	7313
8398	UUGAAUUA G UCAGAGGA	2517	TCCTCTGA GGCTAGCTACAACGA TAATTCAA	7314
8390	GUCAGAGG A CCCCCGAU	2518	ATCGGGGG GGCTAGCTACAACGA CCTCTGAC	7315
8383	GACCCCCG A UAUAAAGC	2519	GCTTTATA GGCTAGCTACAACGA CGGGGGTC	7316
8381	CCCCCGAU A UAAAGCCG	2520	CGGCTTTA GGCTAGCTACAACGA ATCGGGGG	7317
8376	GAUAUAAA G CCGCUCUG	2521	CAGAGCGG GGCTAGCTACAACGA TTTATATC	7318
8373	AUAAAGCC G CUCUGUGA	2522	TCACAGAG GGCTAGCTACAACGA GGCTTTAT	7319
8368	GCCGCUCU G UGAGCGAC	2523	GTGCTCA GGCTAGCTACAACGA AGAGCGGC	7320
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8361	UGUGAGCG A CCUUAUGG	2525	CCATAAGG GGCTAGCTACAACGA CGCTCACA	7322
8356	GCGACCUU A UGGCCUGU	2526	ACAGCCA GGCTAGCTACAACGA AAGGTCGC	7323
8353	ACCUUAUG G CCUGUCUG	2527	CAGACAGG GGCTAGCTACAACGA CATAAGGT	7324
8349	UAUGGCCU G UCUGGCUU	2528	AAGCCAGA GGCTAGCTACAACGA AGGCCATA	7325
8344	CCUGUCUG G CUUCGGGG	2529	CCCCGAAG GGCTAGCTACAACGA CAGACAGG	7326
8335	CUUCGGGG G CCAAGUCA	2530	TGACTTGG GGCTAGCTACAACGA CCCCGAAG	7327
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8327	GCCAAGC A CAACAUUG	2532	CAATGTTG GGCTAGCTACAACGA GACTTGGC	7329
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8310	GUAAAUUG A CUCCUCGA	2537	TCGAGGAG GGCTAGCTACAACGA CAATTTAC	7334
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8291	CGGAUGUC A CUCUCGGU	2542	ACCGAGAG GGCTAGCTACAACGA GACATCCG	7339
8284	CACUCUCG G UGACUGUU	2543	AACAGTCA GGCTAGCTACAACGA CGAGAGTG	7340
8281	UCUCGGUG A CUGUUGAG	2544	CTAACAG GGCTAGCTACAACGA CACCGAGA	7341
8278	CGGUGACU G UUGAGUCG	2545	CGACTCAA GGCTAGCTACAACGA AGTCACCG	7342
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8216	UUCCAGGC A UUCACCAG	2560	CTGGTGAA GGCTAGCTACAACGA GCCTGGAA	7357
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8200	GGAACUCA A CCCGUGC	2563	GCAGCGGG GGCTAGCTACAACGA TGAGTTCC	7360
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8183	CCAGGAGA G UACUGGAA	2566	TTCCAGTA GGCTAGCTACAACGA TCTCCTGG	7363
8181	AGGAGAGU A CUGGAAUC	2567	GATTCCAG GGCTAGCTACAACGA ACTCTCCT	7364
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8129	GAGACCAC G UCGUAAAG	2578	CTTTACGA GGCTAGCTACAACGA GTGGTCTC	7375
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8038	CUGGUUGG A CGCAGAAA	2597	TTTCTGCG GGCTAGCTACAACGA CCAACCAG	7394
8036	GGUUGGAC G CAGAAAC	2598	GTTTTCTG GGCTAGCTACAACGA GTCCAACC	7395
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8024	AAAACCUC A UUUUUUGC	2600	GCAAAAAA GGCTAGCTACAACGA GAGGTTTT	7397
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8014	UUUUUGCC A UGAUGGUG	2602	CACCATCA GGCTAGCTACAACGA GGCAAAAA	7399
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8008	CCAUGAUG G UGGUAUCA	2604	TGATACCA GGCTAGCTACAACGA CATCATGG	7401
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8003	AUGGUGGU A UCAAUUGG	2606	CCAATTGA GGCTAGCTACAACGA ACCACCAT	7403
7999	UGGUAUCA A UUGGUGUC	2607	GACACCAA GGCTAGCTACAACGA TGATACCA	7404
7995	AUCAAUUG G UGUCUCAG	2608	CTGAGACA GGCTAGCTACAACGA CAATTGAT	7405
7993	CAAUUGGU G UCUCAGUG	2609	CACTGAGA GGCTAGCTACAACGA ACCAATTG	7406
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7985	GUCUCAGU G UCUUCCAG	2611	CTGGAAGA GGCTAGCTACAACGA ACTGAGAC	7408
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7973	UCCAGCAA G UCCUCCA	2613	TGGAAGGA GGCTAGCTACAACGA TTGCTGGA	7410
7965	GUCCUCC A CACGGAGC	2614	GCTCCGTG GGCTAGCTACAACGA GGAAGGAC	7411

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7958	CACACGGA G CGGAUGUG	2616	CACATCCG GGCTAGCTACAACGA TCCGTGTG	7413
7954	CGGAGCGG A UGUGGUUG	2617	CAACCACA GGCTAGCTACAACGA CCGCTCCG	7414
7952	GAGCGGAU G UGUUGAC	2618	GTCAACCA GGCTAGCTACAACGA ATCCGCTC	7415
7949	CGGAUGUG G UUGACGGC	2619	GCCGTCAA GGCTAGCTACAACGA CACATCCG	7416
7945	UGUGGUUG A CGGCCCG	2620	CGGGGCCG GGCTAGCTACAACGA CAACCACA	7417
7942	GGUUGACG G CCCCUCUG	2621	CAGCGGGG GGCTAGCTACAACGA CGTCAACC	7418
7937	ACGGCCCC G CUGGAUAG	2622	CTATCCAG GGCTAGCTACAACGA GGGGCCGT	7419
7932	CCCGCUGG A UAGGUUCC	2623	GGAACCTA GGCTAGCTACAACGA CCAGCGGG	7420
7928	CUGGAUAG G UCCCGAC	2624	GTCCGGAA GGCTAGCTACAACGA CTATCCAG	7421
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7919	UUCGGAC G UCCUUUGC	2626	GCAAAGGA GGCTAGCTACAACGA TCCGGAA	7423
7912	CGUCCUUU G CCCCAUAA	2627	TTATGGGG GGCTAGCTACAACGA AAAGGACG	7424
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7888	UGGACCUG G CCGAUGU	2632	ACATTCCG GGCTAGCTACAACGA CAGGTCCA	7429
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7881	GGCCGAU G UGGGGCG	2634	CGCCCCA GGCTAGCTACAACGA ATTCCGCC	7431
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7865	GUCAGUCU G CAGGCUUC	2638	GAAGCCTG GGCTAGCTACAACGA AGACTGAC	7435
7861	GUCUGCAG G CUUCCUCU	2639	AGAGGAAG GGCTAGCTACAACGA CTGCAGAC	7436
7852	CUUCCUCU A CGGAUAGA	2640	TCTATCCG GGCTAGCTACAACGA AGAGGAAG	7437
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7842	GGAUAGAA G UUUAGCCU	2642	AGGCTAAA GGCTAGCTACAACGA TTCTATCC	7439
7837	GAAGUUUA G CCUUAACU	2643	AGTTAAGG GGCTAGCTACAACGA TAACTTC	7440
7831	UAGCCUUA A CUGUGGAC	2644	GTCCACAG GGCTAGCTACAACGA TAAGGCTA	7441
7828	CCUUAACU G UGGACGCC	2645	GGCGTCCA GGCTAGCTACAACGA AGTTAAGG	7442
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7816	ACGCCUUC G CCUUCAUC	2648	GATGAAGG GGCTAGCTACAACGA GAAGGCGT	7445
7810	UCGCCUUC A UCUCUUG	2649	CAAGGAGA GGCTAGCTACAACGA GAAGCGCA	7446
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7781	UAGUGGUC G UCCAGGAC	2656	GTCTGGA GGCTAGCTACAACGA GACCACTA	7453
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7756	UGUCAAAG G UGACCUUC	2661	GAAGGTCA GGCTAGCTACAACGA CTTTGACA	7458
7753	CAAAGGUG A CCUUCUUC	2662	GAAGAAGG GGCTAGCTACAACGA CACCTTTG	7459
7743	CUUCUUCU G CCGCUGGC	2663	GCCAGCGG GGCTAGCTACAACGA AGAAGAAG	7460
7740	CUUCUGCC G CUGGCUUG	2664	CAAGCCAG GGCTAGCTACAACGA GGCAGAAG	7461
7736	UGCCGCU G CUUGCGCU	2665	AGCGCAAG GGCTAGCTACAACGA CAGCGGCA	7462
7732	GCUGGCUU G CGUCGCGA	2666	TCGCGAGG GGCTAGCTACAACGA AAGCCAGC	7463
7730	UGGCUUGC G CUGCGAGA	2667	TCTCGCAG GGCTAGCTACAACGA GCAAGCCA	7464
7727	CUUGCGCU G CGAGAUGU	2668	ACATCTCG GGCTAGCTACAACGA AGCGCAAG	7465
7722	GCUGCGAG A UGUUGUAG	2669	CTACAACA GGCTAGCTACAACGA CTCGCAGC	7466
7720	UGCGAGAU G UGUAGCG	2670	CGTACAA GGCTAGCTACAACGA ATCTCGCA	7467
7717	GAGAUGUU G UAGCGUAG	2671	CTACGCTA GGCTAGCTACAACGA AACATCTC	7468

7714	AUGUUGUA G CGUAGACC	2672	GGTCTACG GGCTAGCTACAACGA TACAACAT	7469
7712	GUUGUAGC G UAGACCAU	2673	ATGGTCTA GGCTAGCTACAACGA GCTACAAC	7470
7708	UAGCGUAG A CCAUGUUG	2674	CAACATGG GGCTAGCTACAACGA CTACGCTA	7471
7705	CGUAGACC A UGUUGUGG	2675	CCACAACA GGCTAGCTACAACGA GGTCTACG	7472
7703	UAGACCAU G UUGUGGUG	2676	CACCACAA GGCTAGCTACAACGA ATGGTCTA	7473
7700	ACCAUGUU G UGGUGACG	2677	CGTCACCA GGCTAGCTACAACGA AACATGGT	7474
7697	AUGUUGUG G UGACGCAG	2678	CTGCGTCA GGCTAGCTACAACGA CACAACAT	7475
7694	UUGUGGUG A CGCAGCAA	2679	TTGCTGCG GGCTAGCTACAACGA CACCACAA	7476
7692	GUGGUGAC G CAGCAAAG	2680	CTTTGCTG GGCTAGCTACAACGA GTCACCAC	7477
7689	GUGACGCA G CAAAGAGU	2681	ACTCTTTG GGCTAGCTACAACGA TGCCTCAC	7478
7682	AGCAAAGA G UUGCUCAA	2682	TTGAGCAA GGCTAGCTACAACGA TCTTTGCT	7479
7679	AAAGAGUU G CUCAACGC	2683	GCGTTGAG GGCTAGCTACAACGA AACTCTTT	7480
7674	GUUGCUCU A CGCGUUGA	2684	TCAACGCG GGCTAGCTACAACGA TGAGCAAC	7481
7672	UGCUCUAC G CGUUGAUG	2685	CATCAACG GGCTAGCTACAACGA GTTGAGCA	7482
7670	CUCAACGC G UUGAUGGG	2686	CCCATCAA GGCTAGCTACAACGA GCGTTGAG	7483
7666	ACGCGUUG A UGGGCAAC	2687	GTTGCCCA GGCTAGCTACAACGA CAACGCGT	7484
7662	GUUGAUGG G CAACUUGC	2688	GCAAGTTG GGCTAGCTACAACGA CCATCAAC	7485
7659	GAUGGGCA A CUUGCUUU	2689	AAAGCAAG GGCTAGCTACAACGA TGCCCATC	7486
7655	GGCAACUU G CUUCCUC	2690	GAGGAAAG GGCTAGCTACAACGA AAGTTGCC	7487
7645	UUUCCUCC G CAGCGCAU	2691	ATGCGCTG GGCTAGCTACAACGA GGAGGAAA	7488
7642	CCUCCGCA G CGCAUGGC	2692	GCCATGCG GGCTAGCTACAACGA TGCGGAGG	7489
7640	UCCGCAGC G CAUGGCGU	2693	ACGCCATG GGCTAGCTACAACGA GCTGCGGA	7490
7638	CGCAGCGC A UGGCGUGA	2694	TCACGCCA GGCTAGCTACAACGA GCGCTGCG	7491
7635	AGCGCAUG G CGUGAUCU	2695	TGATCACG GGCTAGCTACAACGA CATGCGCT	7492
7633	CGCAUGGC G UGAUCAGG	2696	CCTGATCA GGCTAGCTACAACGA GCCATGCG	7493
7630	AUGGCGUG A UCAGGGCG	2697	CGCCCTGA GGCTAGCTACAACGA CACGCCAT	7494
7624	UGAUCAGG G CGCCCGUC	2698	GACGGGCG GGCTAGCTACAACGA CCTGATCA	7495
7622	AUCAGGGC G CCCGUCCA	2699	TGGACGGG GGCTAGCTACAACGA GCCCTGAT	7496
7618	GGGCGCCC G UCCAUGUG	2700	CACATGGA GGCTAGCTACAACGA GGGCGCCC	7497
7614	GCCCGUCC A UGUGUAGG	2701	CCTACACA GGCTAGCTACAACGA GGACGGGC	7498
7612	CCGUCCAU G UGUAGGAC	2702	GTCCTACA GGCTAGCTACAACGA ATGGACGG	7499
7610	GUCCAUGU G UAGGACAU	2703	ATGTCCTA GGCTAGCTACAACGA ACATGGAC	7500
7605	UGUGUAGG A CAUCGAGC	2704	GCTCGATG GGCTAGCTACAACGA CCTACACA	7501
7603	UGUAGGAC A UCGAGCAG	2705	CTGCTCGA GGCTAGCTACAACGA GTCCTACA	7502
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7595	AUCGAGCA G CAGACGAC	2707	GTCGTCTG GGCTAGCTACAACGA TGCTCGAT	7504
7591	AGCAGCAG A CGACAUC	2708	GGATGTCG GGCTAGCTACAACGA GGTCTGCT	7505
7588	AGCAGACG A CAUCCUCG	2709	CGAGGATG GGCTAGCTACAACGA CGTCTGCT	7506
7586	CAGACGAC A UCCUCGCC	2710	GGCGAGGA GGCTAGCTACAACGA GTCGTCTG	7507
7580	ACAUCUC G CCAGCCUC	2711	GAGGCTGG GGCTAGCTACAACGA GAGGATGT	7508
7576	CCUCGCCA G CCUCUUCG	2712	CGAAGAGG GGCTAGCTACAACGA TGGCGAGG	7509
7568	GCCUCUUC G CUCACGGU	2713	ACCGTGAG GGCTAGCTACAACGA GAAGAGGC	7510
7564	CUUCGCUC A CGGUAGAC	2714	GTCTACCG GGCTAGCTACAACGA GAGCGAAG	7511
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7551	AGACCAAG A CCCGUCGC	2717	GCGACGGG GGCTAGCTACAACGA CTTGGTCT	7514
7547	CAAGACCC G UCGUGAG	2718	CTCAGCGA GGCTAGCTACAACGA GGGTCTTG	7515
7544	GACCCGUC G CUGAGAUC	2719	GATCTCAG GGCTAGCTACAACGA GACGGGTC	7516
7538	UCGCUGAG A UCGGGAUC	2720	GATCCCGA GGCTAGCTACAACGA CTCAGCGA	7517
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7524	AUCCCCCG G CUCCCCCU	2722	AGGGGGAG GGCTAGCTACAACGA CGGGGGAT	7519
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7496	AUAGAGGA G UACGACUC	2725	GAGTCGTA GGCTAGCTACAACGA TCCTCTAT	7522
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7491	GGAGUACG A CUCAACGU	2727	ACGTTGAG GGCTAGCTACAACGA CGTACTCC	7524
7486	ACGACUCA A CGUCGGAU	2728	ATCCGACG GGCTAGCTACAACGA TGAGTCGT	7525

7484	GACUCAAC G UCGGAUCC	2729	GGATCCGA GGCTAGCTACAACGA GTTGAGTC	7526
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7474	CGGAUCCU G CGUACCCG	2731	CGGTGACG GGCTAGCTACAACGA AGGATCCG	7528
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7466	GCGUCACC G UCAUUGGA	2734	TCCAATGA GGCTAGCTACAACGA GGTGACGC	7531
7463	UCACCGUC A UUGGAGGU	2735	ACCTCCAA GGCTAGCTACAACGA GACGGTGA	7532
7456	CAUUGGAG G UCUGGUCG	2736	CGACCAGA GGCTAGCTACAACGA CTCCAATG	7533
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7435	GGGCGGUU G CCGUACCU	2740	AGGTACGG GGCTAGCTACAACGA AACCGCCC	7537
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7417	UAUCAGCG G CCGAUGAU	2745	ATCATCGG GGCTAGCTACAACGA CGCTGATA	7542
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7314	UGGAGGUG G UAUUGGAG	2766	CTCCAATA GGCTAGCTACAACGA CACCTCCA	7563
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7293	CUUGGCAG G UGGCAAUG	2770	CATTGCCA GGCTAGCTACAACGA CTGCCAAG	7567
7290	GGCAGGUG G CAAUGGGC	2771	GCCCATTG GGCTAGCTACAACGA CACCTGCC	7568
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7275	GCACCCGU G UACCACCG	2776	CGGTGGTA GGCTAGCTACAACGA ACGGGTGC	7573
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7270	CGUGUACC A CCGGAGGG	2778	CCCTCCGG GGCTAGCTACAACGA GGTACACG	7575
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7250	UAGUCUGG G UCUUCCCA	2782	TGGAAGA GGCTAGCTACAACGA CCAGACTA	7579
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7070	GACUCCAC G CGAGUGAU	2816	ATCACTCG GGCTAGCTACAACGA GTGGAGTC	7613
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7051	UACCGCCC A UCUCUGC	2822	GCAGGAGA GGCTAGCTACAACGA GGGCGGTA	7619
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7031	CACAGGAG G UUGCCUC	2826	GAGGCCAA GGCTAGCTACAACGA CTCCTGTG	7623
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7021	UGGCCUCG A UGAGGUCA	2828	TGACCTCA GGCTAGCTACAACGA CGAGGCCA	7625
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6986	UGGGUAAU G UAUGUCGC	2836	GCGACATA GGCTAGCTACAACGA ATTACCCA	7633
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6787	UGAGCCCG A CCUGGAAU	2881	ATTCCAGG GGCTAGCTACAACGA CGGGCTCA	7678
6780	GACCUGGA A UGUGACCU	2882	AGGTCACA GGCTAGCTACAACGA TCCAGGTC	7679
6778	CCUGGAAU G UGACCUCC	2883	GGAGGTCA GGCTAGCTACAACGA ATTCCAGG	7680
6775	GGAUUGUG A CCUCCUCC	2884	GGAGGAGG GGCTAGCTACAACGA CACATTCC	7681
6765	CUCCUCCC G UAGGAGAG	2885	CTCTCCTA GGCTAGCTACAACGA GGGAGGAG	7682
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6752	AGAGGUCC A CACGCCGG	2887	CCGGCGTG GGCTAGCTACAACGA GGACCTCT	7684
6750	AGGUCCAC A CGCCGGAG	2888	CTCCGGCG GGCTAGCTACAACGA GTGGACCT	7685
6748	GUCCACAC G CCGGAGCG	2889	CGCTCCGG GGCTAGCTACAACGA GTGTGGAC	7686
6742	ACGCCGGA G CGUUUCUG	2890	CAGAAACG GGCTAGCTACAACGA TCCGGCGT	7687
6740	GCCGGAGC G UUCUGUG	2891	CACAGAAA GGCTAGCTACAACGA GCTCCGGC	7688
6734	GCGUUUCU G UGCAGGCG	2892	CGCCTGCA GGCTAGCTACAACGA AGAAACGC	7689
6732	GUUUCUGU G CAGGCGUA	2893	TACGCCTG GGCTAGCTACAACGA ACAGAAAC	7690
6728	CUGUGCAG G CGUACCCC	2894	GGGGTACG GGCTAGCTACAACGA CTGCACAG	7691
6726	GUGCAGGC G UACCCCAU	2895	ATGGGGTA GGCTAGCTACAACGA GCCTGCAC	7692
6724	GCAGGCGU A CCCCACU	2896	GGATGGGG GGCTAGCTACAACGA ACGCCTGC	7693
6719	CGUACCCC A UCCACUUC	2897	GAAGTGGA GGCTAGCTACAACGA GGGGTACG	7694
6715	CCCCAUCC A CUUCCGUG	2898	CACGGAAG GGCTAGCTACAACGA GGATGGGG	7695
6709	CCACUUCG G UGAAGAAU	2899	ATTCTTCA GGCTAGCTACAACGA GGAAGTGG	7696

6702	CGUGAAGA A UUCGGGGG	2900	CCCCCGAA GGCTAGCTACAACGA TCTTCACG	7697
6693	UUCGGGGG G CGGAACCU	2901	AGGTTCCG GGCTAGCTACAACGA CCCCCGAA	7698
6688	GGGGCGGA A CCUGGCAC	2902	GTGCCAGG GGCTAGCTACAACGA TCCGCCCC	7699
6683	GGAACCUG G CACGGGCA	2903	TGCCCCGTG GGCTAGCTACAACGA CAGGTTCC	7700
6681	AACCUGGC A CGGGCAUU	2904	AATGCCCC GGCTAGCTACAACGA GCCAGGTT	7701
6677	UGGCACGG G CAUUUUAC	2905	GTAAATG GGCTAGCTACAACGA CCGTGCCA	7702
6675	GCACGGGC A UUUUACGU	2906	ACGTAAAA GGCTAGCTACAACGA GCCCGTGC	7703
6670	GGCAUUUU A CGUUGUCA	2907	TGACAACG GGCTAGCTACAACGA AAAATGCC	7704
6668	CAUUUUAC G UUGUCAGU	2908	ACTGACAA GGCTAGCTACAACGA GTAAATG	7705
6665	UUUACGUU G UCAGUGGU	2909	ACCACTGA GGCTAGCTACAACGA AACGTAAA	7706
6661	CGUUGUCA G UGGUCAUG	2910	CATGACCA GGCTAGCTACAACGA TGACAACG	7707
6658	UGUCAGUG G UCAUGCCC	2911	GGGCATGA GGCTAGCTACAACGA CACTGACA	7708
6655	CAGUGGUC A UGCCCCGUC	2912	GACGGGCA GGCTAGCTACAACGA GACCATG	7709
6653	GUGGUCAU G CCCGUCAC	2913	GTGACGGG GGCTAGCTACAACGA ATGACCAC	7710
6649	UCAUGCCC G UCACGUAG	2914	CTACGTGA GGCTAGCTACAACGA GGGCATGA	7711
6646	UGCCCCGUC A CGUAGUGG	2915	CCACTACG GGCTAGCTACAACGA GACGGGCA	7712
6644	CCCGUCAC G UAGUGGAA	2916	TTCCACTA GGCTAGCTACAACGA GTGACGGG	7713
6641	GUCACGUA G UGGAAAUC	2917	GATTTCCA GGCTAGCTACAACGA TACGTGAC	7714
6635	UAGUGGAA A UCCCCCAC	2918	GTGGGGGA GGCTAGCTACAACGA TTCCACTA	7715
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6622	CCACCCGC G UAACCUCC	2921	GGAGTTA GGCTAGCTACAACGA GCGGGTGG	7718
6619	CCGCGGUA A CCUCCACG	2922	CGTGGAGG GGCTAGCTACAACGA TACGCGGG	7719
6613	UAACCUCC A CGUACUCC	2923	GGAGTACG GGCTAGCTACAACGA GGAGTTA	7720
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6598	CCUCAGCG G CCACCCGC	2927	GCGGGTGG GGCTAGCTACAACGA CGCTGAGG	7724
6595	CAGCGGCC A CCCGCCAU	2928	ATGGCGGG GGCTAGCTACAACGA GGCCGCTG	7725
6591	GGCCACCC G CCAUAGCG	2929	CGCTATGG GGCTAGCTACAACGA GGGTGGCC	7726
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6583	GCCAUAGC G CCCUAGAA	2932	TTCTAGGG GGCTAGCTACAACGA GCTATGGC	7729
6575	GCCCUAGA A UAGUUUGG	2933	CCAACTA GGCTAGCTACAACGA TCTAGGGC	7730
6572	CUAGAAUA G UUUGGCGC	2934	CGGCCAAA GGCTAGCTACAACGA TATTCTAG	7731
6567	AUAGUUUG G CGCCGGGG	2935	CCCCGGCG GGCTAGCTACAACGA CAAACTAT	7732
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6551	GAGGGUGU G CAGGGGCC	2939	GGCCCCCTG GGCTAGCTACAACGA ACACCCTC	7736
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6538	GGCCCGUG G UGUAGCG	2942	CGCATACA GGCTAGCTACAACGA CACGGGCC	7739
6536	CCCGUGGU G UAUGCGUU	2943	AACGCATA GGCTAGCTACAACGA ACCACGGG	7740
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6500	CACGUGUU G CUACAGGU	2955	ACCTGTAG GGCTAGCTACAACGA AACACGTG	7752
6497	GUGUUGCU A CAGGUCUU	2956	AAGACCTG GGCTAGCTACAACGA AGCAACAC	7753

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6478	GCCCCACG A UCCUCAUG	2960	CATGAGGA GGCTAGCTACAACGA CGTCGGGC	7757
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6467	CUCAUGGA A CCGUUCUU	2962	AAGAACGG GGCTAGCTACAACGA TCCATGAG	7759
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6424	AUGGGCAG G UGGUUGC	2974	GCAAACCA GGCTAGCTACAACGA CTGCCCAT	7771
6421	GGCAGGUG G UUUGCAUG	2975	CATGCAAA GGCTAGCTACAACGA CACCTGCC	7772
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6386	ACCCCCU G UACCCACG	2983	CGTGGGTA GGCTAGCTACAACGA AGGGGGGT	7780
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6358	AGAAAGGG A CUCCCGGC	2989	GCCGGGAG GGCTAGCTACAACGA CCCTTTCT	7786
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6348	UCCCGGCA A CCGCGGCA	2991	TGCCGCGG GGCTAGCTACAACGA TGCCGGGA	7788
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6342	CAACCGCG G CAGGAGCU	2993	AGTCTCTG GGCTAGCTACAACGA CGGTGTTG	7790
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6319	GAAGCCAG G UCUUGAAG	2997	CTTCAAGA GGCTAGCTACAACGA CTGGCTTC	7794
6311	GUCUUGAA G UCAGUCA	2998	TTGACTGA GGCTAGCTACAACGA TTCAAGAC	7795
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6303	GUCAGUCA A CACCGUGC	3000	GCACGGTG GGCTAGCTACAACGA TGACTGAC	7797
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6294	CACCGUGC A UAUCCAGU	3004	ACTGGATA GGCTAGCTACAACGA GCACGGTG	7801
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6245	GGCGUGGA G CAGUCCUC	3016	GAGGACTG GGCTAGCTACAACGA TCCACGCC	7813
6242	GUGGAGCA G UCCUCAU	3017	AATGAGGA GGCTAGCTACAACGA TGCTCCAC	7814
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6210	CCUCCUCA G CAGCUGAG	3023	CTCAGCTG GGCTAGCTACAACGA TGAGGAGG	7820
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6191	AUGGUGAG G CUGGAGAG	3028	CTCTCCAG GGCTAGCTACAACGA CTCACCAT	7825
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6168	UGUGACGC G CGCCGUG	3034	CAGCGGCG GGCTAGCTACAACGA GCGTCACA	7831
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6143	UCAGGCAC A UAGUGCGU	3042	ACGCACTA GGCTAGCTACAACGA GTGCCTGA	7839
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6048	AUGCCGAC G CAGUAUCG	3068	CGATACTG GGCTAGCTACAACGA GTCGGCAT	7865
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5984	GGGAGUAA G UUGACCAG	3084	CTGGTCAA GGCTAGCTACAACGA TTA CTCCC	7881
5980	GUAAGUUG A CCAGGUCC	3085	GGACCTGG GGCTAGCTACAACGA CAACTTAC	7882
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5917	CACCCGCC A CUCCUGCU	3098	AGCAGGAG GGCTAGCTACAACGA GGCGGGTG	7895
5911	CCACUCCU G CUCCAUA	3099	CTATGGAG GGCTAGCTACAACGA AGGAGTGG	7896
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5866	CAAGGCCU A UGCUGCCA	3109	TGGCAGCA GGCTAGCTACAACGA AGGCCTTG	7906
5864	AGGCCUAU G CUGCCAAC	3110	GTTGGCAG GGCTAGCTACAACGA ATAGCCCT	7907
5861	CCUAUGCU G CCAACAGC	3111	GCTGTTGG GGCTAGCTACAACGA AGCATAGG	7908
5857	UGCUGCCA A CAGCCGCG	3112	CGCGGCTG GGCTAGCTACAACGA TGGCAGCA	7909
5854	UGCCAACA G CCGGCCCA	3113	TGGCGCGG GGCTAGCTACAACGA TGTGGCA	7910
5851	CAACAGCC G CGCCAGCG	3114	CGCTGGCG GGCTAGCTACAACGA GGCTGTTG	7911
5849	ACAGCCGC G CCAGCGAU	3115	ATCGCTGG GGCTAGCTACAACGA GCGGCTGT	7912
5845	CCGCGCCA G CGAUGCCG	3116	CGGCATCG GGCTAGCTACAACGA TGGCGCGG	7913
5842	CGCCAGCG A UGCCGCGG	3117	CGCCGGCA GGCTAGCTACAACGA CGCTGGCG	7914
5840	CCAGCGAU G CCGGCGCC	3118	GGCGCCGG GGCTAGCTACAACGA ATCGCTGG	7915
5836	CGAUGCCG G CGCCCACG	3119	CGTGGGCG GGCTAGCTACAACGA CGGCATCG	7916
5834	AUGCCGGC G CCCACGAA	3120	TTCGTGGG GGCTAGCTACAACGA GCCGCGAT	7917
5830	CGGCGCCC A CGAAGGCC	3121	GGCCTTCG GGCTAGCTACAACGA GGGCGCCG	7918
5824	CCACGAAG G CCGAAACG	3122	CGTTTCGG GGCTAGCTACAACGA CTTCTGGG	7919
5818	AGGCCGAA A CGGCUCUG	3123	CAGAGCCG GGCTAGCTACAACGA TTCGCGCT	7920
5815	CCGAAACG G CUCUGGGG	3124	CCCCAGAG GGCTAGCTACAACGA CGTTTCGG	7921
5803	UGGGGGGA G CGAGUUGG	3125	CCAACTCG GGCTAGCTACAACGA TCCCCCA	7922
5799	GGGAGCGA G UUGGGCGG	3126	CCGCCCAA GGCTAGCTACAACGA TCGTCCC	7923
5794	CGAGUUGG G CGGCCACC	3127	GGTGGCCG GGCTAGCTACAACGA CCAACTCG	7924

5791	GUUGGGCG G CCACCCAC	3128	GTGGGTGG GGCTAGCTACAACGA CGCCCAAC	7925
5788	GGGCGGCC A CCCACCCU	3129	AGGGTGGG GGCTAGCTACAACGA GGCCGCC	7926
5784	GGCCACCC A CCCUCCA	3130	TGGGAGGG GGCTAGCTACAACGA GGGTGGCC	7927
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5771	CCCAAGAU G UUGAACAG	3132	CTGTTCAA GGCTAGCTACAACGA ATCTTGGG	7929
5766	GAUGUUGA A CAGGAGGG	3133	CCCTCCTG GGCTAGCTACAACGA TCAACATC	7930
5758	ACAGGAGG G UGCUUUGG	3134	CCAAAGCA GGCTAGCTACAACGA CCTCCTGT	7931
5756	AGGAGGGU G CUUUGGGU	3135	ACCCAAAG GGCTAGCTACAACGA ACCCTCCT	7932
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5738	GUGAGCGG G CUGGUGAU	3139	ATCACCAG GGCTAGCTACAACGA CCGCTCAC	7936
5734	GCGGGCUG G UGAUGGAG	3140	CTCCATCA GGCTAGCTACAACGA CAGCCCGC	7937
5731	GGCUGGUG A UGGAGGCU	3141	AGCCTCCA GGCTAGCTACAACGA CACCAGCC	7938
5725	UGAUGGAG G CUGUGAAU	3142	ATTACAG GGCTAGCTACAACGA CTCCATCA	7939
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5718	GGCUGUGA A UGCCAUCA	3144	TGATGGCA GGCTAGCTACAACGA TCACAGCC	7941
5716	CUGUGAAU G CCAUCAAU	3145	ATTGATGG GGCTAGCTACAACGA ATTACAG	7942
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5709	UGCCAUCA A UGAUGCUA	3147	TAGCATCA GGCTAGCTACAACGA TGATGGCA	7944
5706	CAUCAAU G UGCUAUCG	3148	CGATAGCA GGCTAGCTACAACGA CATTGATG	7945
5704	UCAAUCAU G CUAUCGCG	3149	CGCGATAG GGCTAGCTACAACGA ATCATTGA	7946
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5680	CAGGCAGA G UGGACAAG	3154	CTTGTTCA GGCTAGCTACAACGA TCTGCCTG	7951
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5672	GUGGACAA G CCUGCUAG	3156	CTAGCAGG GGCTAGCTACAACGA TTGTCCAC	7953
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5661	UGCUAGGU A CUGUAUCC	3159	GGATACAG GGCTAGCTACAACGA ACCTAGCA	7956
5658	UAGGUACU G UAUCCCGC	3160	GCGGGATA GGCTAGCTACAACGA AGTACCTA	7957
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5651	UGUAUCCC G CUGAUGAA	3162	TTCATCAG GGCTAGCTACAACGA GGGATACA	7959
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5631	CCACAUGU G CUUCGCCC	3168	GGGCGAAG GGCTAGCTACAACGA ACATGTGG	7965
5626	UGUGCUUC G CCCAGAAA	3169	TTTCTGGG GGCTAGCTACAACGA GAAGCACA	7966
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5587	AUCCACC A CGGGAGCA	3176	TGCTCCCG GGCTAGCTACAACGA GGTGGAAT	7973
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5560	CUUGGUUG G UGGCUGUU	3182	AACAGCCA GGCTAGCTACAACGA CAACCAAG	7979
5557	GGUUGGUG G CUGUUUGC	3183	GCAAACAG GGCTAGCTACAACGA CACCAACC	7980
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5536	AUCCGAGC G CCUUCUGC	3189	GCAGAAGG GGCTAGCTACAACGA GCTCGGAT	7986
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5459	UCCAUCUC A UCGAACUC	3206	GAGTTCGA GGCTAGCTACAACGA GAGATGGA	8003
5454	CUCAUCGA A CUCCUGGU	3207	ACCAGGAG GGCTAGCTACAACGA TCGATGAG	8004
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5338	CUGCCAGG A CGCCACCU	3234	AGGTGGCG GGCTAGCTACAACGA CCTGGCAG	8031
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4956	AGCCCGCA A CCUAACGG	3330	CCGTTAGG GGCTAGCTACAACGA TGCGGGCT	8127
4951	GCAACCUA A CGGAGGUC	3331	GACCTCCG GGCTAGCTACAACGA TAGGTTGC	8128
4945	UAACGGAG G UCUCGGCG	3332	CGCCGAGA GGCTAGCTACAACGA CTCGGTTA	8129
4939	AGGUCUCG G CGGGCGUG	3333	CACGCCCG GGCTAGCTACAACGA CGAGCCT	8130
4935	CUCGGCGG G CGUGAGCU	3334	AGCTCACG GGCTAGCTACAACGA CCGCCGAG	8131
4933	CGGCGGGC G UGAGCUCG	3335	CGAGCTCA GGCTAGCTACAACGA GCCCGCG	8132
4929	GGGCGUGA G CUCGUACC	3336	GGTACGAG GGCTAGCTACAACGA TCACGCC	8133
4925	GUGAGCUC G UACCAAGC	3337	GCTTGGTA GGCTAGCTACAACGA GAGCTCAC	8134
4923	GAGCUCGU A CCAAGCAC	3338	GTGCTTGG GGCTAGCTACAACGA ACGAGCTC	8135
4918	CGUACCAA G CACAUCCC	3339	GGGATGTG GGCTAGCTACAACGA TTGGTACG	8136
4916	UACCAAGC A CAUCCCGC	3340	GCGGGATG GGCTAGCTACAACGA GCTTGGTA	8137
4914	CCAAGCAC A UCCCGCGU	3341	ACGCGGGA GGCTAGCTACAACGA GTGCTTGG	8138
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4904	CCCGCGUC A UAGCACUC	3344	GAGTGCTA GGCTAGCTACAACGA GACGCGGG	8141
4901	GCGUCAUA G CACUCACA	3345	TGTGAGTG GGCTAGCTACAACGA TATGACGC	8142
4899	GUCAUAGC A CUCACACA	3346	TGTGTGAG GGCTAGCTACAACGA GCTATGAC	8143
4895	UAGCACUC A CACAGGAC	3347	GTCCTGTG GGCTAGCTACAACGA GAGTGCTA	8144
4893	GCACUCAC A CAGGACCG	3348	CGGTCCTG GGCTAGCTACAACGA GTGAGTGC	8145
4888	CACACAGG A CCGAGGAG	3349	CTCCTCGG GGCTAGCTACAACGA CCTGTGTG	8146
4880	ACCGAGGA G UCGAACAU	3350	ATGTTTGA GGCTAGCTACAACGA TCCTCGGT	8147
4875	GGAGUCGA A CAUGCCCG	3351	CGGGCATG GGCTAGCTACAACGA TCGACTCC	8148
4873	AGUCGAAC A UGCCCCGAA	3352	TTCGGGCA GGCTAGCTACAACGA GTTCGACT	8149
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4863	GCCCCAAG G CCGCUCUC	3354	GAGAGCGG GGCTAGCTACAACGA CTTGCGGC	8151
4860	CGAAGGCC G CUCUCCUG	3355	CAGGAGAG GGCTAGCTACAACGA GGCCTTCG	8152

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4846	CUGGAGUC A CAAACCUG	3357	CAGGTTTG GGCTAGCTACAACGA GACTCCAG	8154
4842	AGUCACAA A CCUGUAUA	3358	TATACAGG GGCTAGCTACAACGA TTGTGACT	8155
4838	ACAAACCU G UUAUAGCC	3359	GGCATATA GGCTAGCTACAACGA AGGTTTGT	8156
4836	AAACCUGU A UAUGCCUC	3360	GAGGCATA GGCTAGCTACAACGA ACAGGTTT	8157
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4788	CGAGCGGG A CACUGCGU	3370	ACGCAGTG GGCTAGCTACAACGA CCCGCTCG	8167
4786	AGCGGGAC A CUGCGUCU	3371	AGACGCAG GGCTAGCTACAACGA GTCCCGCT	8168
4783	GGGACACU G CGUCUUGG	3372	CCAAGACG GGCTAGCTACAACGA AGTGTCCC	8169
4781	GACACUGC G UCUUGGGG	3373	CCCCAAGA GGCTAGCTACAACGA GCAGTGTC	8170
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4768	GGGGCAGG G UCGUCGUC	3376	GACGACGA GGCTAGCTACAACGA CGTGCCCC	8173
4765	GCACGGUC G UCGUCUCA	3377	TGAGACGA GGCTAGCTACAACGA GACCGTGC	8174
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4753	UCUCAAUG G UGAAGGUA	3380	TACCTTCA GGCTAGCTACAACGA CATTGAGA	8177
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4624	CCCCGCUG G CCGGUAUG	3415	CATACCGG GGCTAGCTACAACGA CAGCGGGG	8212
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4186	UGGUCCUU A CCCAGUU	3523	AACTGGGG GGCTAGCTACAACGA AAGGACCA	8320
4180	UUACCCCA G UUCUGAUG	3524	CATCAGAA GGCTAGCTACAACGA TGGGGTAA	8321
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4078	ACCCUUGG G CUGCAUUA	3550	ATATGCAG GGCTAGCTACAACGA CCAAGGGT	8347
4075	CUUGGGCU G CAUAUGCA	3551	TGCATATG GGCTAGCTACAACGA AGCCCAAG	8348
4073	UGGGCUGC A UAUGCAGC	3552	GCTGCATA GGCTAGCTACAACGA GCAGCCCA	8349
4071	GGCUGCAU A UGCAGCCG	3553	CGGCTGCA GGCTAGCTACAACGA ATGCAGCC	8350
4069	CUGCAUUA G CAGCCGGU	3554	ACCGGCTG GGCTAGCTACAACGA ATATGCAG	8351
4066	CAUAUGCA G CCGGUACC	3555	GGTACCGG GGCTAGCTACAACGA TGCATATG	8352
4062	UGCAGCCG G UACCUUAG	3556	CTAAGGTA GGCTAGCTACAACGA CGGCTGCA	8353
4060	CAGCCGGU A CCUUAGUG	3557	CACTAAGG GGCTAGCTACAACGA ACCGGCTG	8354
4054	GUACCUUA G CUCUCUUG	3558	CAAGAGCA GGCTAGCTACAACGA TAAGGTAC	8355
4052	ACCUUAGU G CUCUUGCC	3559	GGCAAGAG GGCTAGCTACAACGA ACTAAGGT	8356
4046	GUGCUCUU G CCGCUGCC	3560	GGCAGCGG GGCTAGCTACAACGA AAGAGCAC	8357
4043	CUCUUGCC G CUGCCAGU	3561	ACTGGCAG GGCTAGCTACAACGA GGCAAGAG	8358
4040	UUGCCGCU G CCAGUGGG	3562	CCCCTGGG GGCTAGCTACAACGA AGCGGCAA	8359
4036	CGCUGCCA G UGGGAGCG	3563	CGCTCCCA GGCTAGCTACAACGA TGGCAGCG	8360
4030	CAGUGGGA G CGUGUAGG	3564	CCTACACG GGCTAGCTACAACGA TCCCCTG	8361
4028	GUGGGAGC G UGUAGGUG	3565	CACCTACA GGCTAGCTACAACGA GCTCCAC	8362
4026	GGGAGCGU G UAGGUGGG	3566	CCCACCTA GGCTAGCTACAACGA ACGCTCCC	8363
4022	GCGUGUAG G UGGGCCAC	3567	GTGGCCCA GGCTAGCTACAACGA CTACACGC	8364
4018	GUAGGUGG G CCACUUGG	3568	CCAAGTGG GGCTAGCTACAACGA CCACCTAC	8365
4015	GGUGGGCC A CUUGGAU	3569	ATTCCAAG GGCTAGCTACAACGA GGCCACC	8366
4008	CACUUGGA A UGUCUGCG	3570	CGCAGACA GGCTAGCTACAACGA TCCAAGTG	8367
4006	CUUGGAU G UCUGCGGU	3571	ACCGCAGA GGCTAGCTACAACGA ATTCCAAG	8368
4002	GAAUGUCU G CGGUACGG	3572	CCGTACCG GGCTAGCTACAACGA AGACATTC	8369
3999	UGUCUGCG G UACGGCUG	3573	CAGCCGTA GGCTAGCTACAACGA CGCAGACA	8370
3997	UCUGCGGU A CGGCUGGG	3574	CCCAGCCG GGCTAGCTACAACGA ACCGCAGA	8371
3994	GCGGUACG G CUGGGGGG	3575	CCCCCCAG GGCTAGCTACAACGA CGTACCGC	8372
3984	UGGGGGGG A CGAGUUGU	3576	ACAACTCG GGCTAGCTACAACGA CCCCCCA	8373
3980	GGGGACGA G UUGUCCGU	3577	ACGGACAA GGCTAGCTACAACGA TCGTCCCC	8374
3977	GACGAGUU G UCCGUGAA	3578	TTCACGGA GGCTAGCTACAACGA AACTCGTC	8375
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3967	CCGUUAG A CCGGGGAC	3580	GTCCCCGG GGCTAGCTACAACGA CTTACGG	8377
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3957	CGGGGACC G CAUGGUAG	3582	CTACCATG GGCTAGCTACAACGA GGTCCCCG	8379
3955	GGGACCGC A UGGUAGUU	3583	AACTACCA GGCTAGCTACAACGA GCGGTCCC	8380

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3943	UAGUUUCC A UAGACUCA	3586	TGAGTCTA GGCTAGCTACAACGA GGAAACTA	8383
3939	UUCCAUG A CUCAACGG	3587	CCGTTGAG GGCTAGCTACAACGA CTATGGAA	8384
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3930	CUCAACGG G UACAAAGU	3589	ACTTTGTA GGCTAGCTACAACGA CCGTTGAG	8386
3928	CAACGGGU A CAAAGUCC	3590	GGACTTTG GGCTAGCTACAACGA ACCCGTTG	8387
3923	GGUACAAA G UCCACCGC	3591	GCGGTGGA GGCTAGCTACAACGA TTTGTACC	8388
3919	CAAAGUCC A CCGCCUUC	3592	GAAGGCGG GGCTAGCTACAACGA GGACTTTG	8389
3916	AGUCCACC G CCUUCGCA	3593	TGCGAAGG GGCTAGCTACAACGA GGTGGACT	8390
3910	CCGCCUUC G CAACCCCC	3594	GGGGGTTG GGCTAGCTACAACGA GAAGGCGG	8391
3907	CCUUCGCA A CCCCCCGG	3595	CCGGGGGG GGCTAGCTACAACGA TGCGAAGG	8392
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3896	CCCCGGGU G CACACAGC	3597	GCTGTGTG GGCTAGCTACAACGA ACCCGGGG	8394
3894	CCGGGUGC A CACAGCAG	3598	CTGTGTGT GGCTAGCTACAACGA GCACCCGG	8395
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3889	UGCACACA G CAGCCCGG	3600	CCGGGCTG GGCTAGCTACAACGA TGTGTGCA	8397
3886	ACACAGCA G CCCGGAAG	3601	CTTCCGGG GGCTAGCTACAACGA TGCTGTGT	8398
3877	CCCGGAAG A UGCCCACA	3602	TGTGGGCA GGCTAGCTACAACGA CTTCCGGG	8399
3875	CGGAAGAU G CCCACAAC	3603	GTTGTGGG GGCTAGCTACAACGA ATCTTCCG	8400
3871	AGAUGCCC A CAACGUGC	3604	GCACGTTG GGCTAGCTACAACGA GGGCATCT	8401
3868	UGCCCACA A CGUGCCCC	3605	GGGGCAGG GGCTAGCTACAACGA TGTGGGCA	8402
3866	CCCACAAC G UGCCCCGA	3606	TCGGGGCA GGCTAGCTACAACGA GTTGTGGG	8403
3864	CACAACGU G CCCCGAAG	3607	CTTCGGGG GGCTAGCTACAACGA ACGTTGTG	8404
3854	CCCGAAGG G CAGAGCAG	3608	CTGCTCTG GGCTAGCTACAACGA CCTTCGGG	8405
3849	AGGGCAGA G CAGUGGAC	3609	GTCCACTG GGCTAGCTACAACGA TCTGCCCT	8406
3846	GCAGAGCA G UGGACCGC	3610	GCGGTCCA GGCTAGCTACAACGA TGCTCTGC	8407
3842	AGCAGUGG A CCGCCCGA	3611	TCGGGCGG GGCTAGCTACAACGA CCACTGCT	8408
3839	AGUGGACC G CCCGAGGA	3612	TCCTCGGG GGCTAGCTACAACGA GGTCCACT	8409
3830	CCCGAGGA G CCCUCAA	3613	TTGAAGGG GGCTAGCTACAACGA TCCTCGGG	8410
3821	CCCUCAA A UAGGAGAU	3614	ATCTCCTA GGCTAGCTACAACGA TTGAAGGG	8411
3814	AGUAGGAG A UGGGCCUG	3615	CAGGCCCA GGCTAGCTACAACGA CTCTACT	8412
3810	GGAGAUUG G CCUGGGGG	3616	CCCCCAGG GGCTAGCTACAACGA CCATCTCC	8413
3801	CCUGGGGG A UAGUAAGC	3617	GCTTACTA GGCTAGCTACAACGA CCCCCAGG	8414
3798	GGGGGAUA G UAAGCUCC	3618	GGAGCTTA GGCTAGCTACAACGA TATCCCC	8415
3794	GAUAGUAA G CUCCCCU	3619	AGGGGGAG GGCTAGCTACAACGA TTACTATC	8416
3785	CUCCCCU G CUGUCACC	3620	GGTGACAG GGCTAGCTACAACGA AGGGGGAG	8417
3782	CCCUGCU G UCACCCCG	3621	CGGGGTGA GGCTAGCTACAACGA AGCAGGGG	8418
3779	CUGCUGUC A CCCC GCCG	3622	CGGCGGGG GGCTAGCTACAACGA GACAGCAG	8419
3774	GUCACCCC G CCGGCGCA	3623	TGCGCCGG GGCTAGCTACAACGA GGGGTGAC	8420
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3760	GCACCGGA A UGACAUCA	3627	TGATGTCA GGCTAGCTACAACGA TCCGGTGC	8424
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3747	AUCAGCGU G UCUCGUGA	3632	TCACGAGA GGCTAGCTACAACGA ACGTGAT	8429
3742	CGUGUCUC G UGACCAAG	3633	CTTGGTCA GGCTAGCTACAACGA GAGACACG	8430
3739	GUCUCGUG A CCAAGUAA	3634	TTACTTGG GGCTAGCTACAACGA CACGAGAC	8431
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3728	AAGUAAAG G UCCGAGCC	3636	GGCTCGGA GGCTAGCTACAACGA CTTTACTT	8433
3722	AGGUCCGA G CCGCCGCA	3637	TGCGGCGG GGCTAGCTACAACGA TCGGACCT	8434
3719	UCCGAGCC G CCGCAGGU	3638	ACCTGCGG GGCTAGCTACAACGA GGCTCGGA	8435
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3705	GGUGCAUG G UGUCAAGG	3643	CCTTGACA GGCTAGCTACAACGA CATGCACC	8440
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3566	CACACGCC G UUGACGCA	3678	TGCGTCAA GGCTAGCTACAACGA GGCGTGTG	8475
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3488	UUGUCCCG G CCCGUGAG	3694	CTCACGGG GGCTAGCTACAACGA CGGGACAA	8491
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3385	GACUGUCG G CUGGUCCU	3719	AGGACCAG GGCTAGCTACAACGA CGACAGTC	8516
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3334	GUAGACCC A UAAUGAUG	3727	CATCATTA GGCTAGCTACAACGA GGGTCTAC	8524
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3277	UGAUUCC A UGUCGGAG	3741	CTCCGACA GGCTAGCTACAACGA GGAAATCA	8538
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3247	CGACCGCU A CCGCCAGG	3748	CCTGGCGG GGCTAGCTACAACGA AGCGGTCTG	8545
3244	CCGCUACC G CCAGGUCU	3749	AGACCTGG GGCTAGCTACAACGA GGTCGCGG	8546
3239	ACCGCCAG G UCUCGUAG	3750	CTACGAGA GGCTAGCTACAACGA CTGGCGGT	8547
3234	CAGGUCUC G UAGACCUG	3751	CAGGTCTA GGCTAGCTACAACGA GAGACCTG	8548
3230	UCUCGUAG A CCUGUGUG	3752	CACACAGG GGCTAGCTACAACGA CTACGAGA	8549
3226	GUAGACCU G UUGGGGCC	3753	GGCCCCA GGCTAGCTACAACGA AGGTCTAC	8550
3224	AGACCUGU G UGGGCCCA	3754	TGGGCCCA GGCTAGCTACAACGA ACAGGTCT	8551

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3162	UUCGGCCA A CUUCAUGA	3769	TCATGAAG GGCTAGCTACAACGA TGGCCGAA	8566
3157	CCAACUUC A UGAAGGCC	3770	GGCCTTCA GGCTAGCTACAACGA GAAGTTGG	8567
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3148	UGAAGGCC A UUUGGACA	3772	TGTCCAAA GGCTAGCTACAACGA GGCCTTCA	8569
3142	CCAUUUGG A CAUAUUGC	3773	GCAATATG GGCTAGCTACAACGA CCAAATGG	8570
3140	AUUUGGAC A UAUUGCCC	3774	GGGCAATA GGCTAGCTACAACGA GTCCAAAT	8571
3138	UUGGACAU A UUGCCCCC	3775	GGGGGCAA GGCTAGCTACAACGA ATGTCCAA	8572
3135	GACAUAAU G CCCCCCAC	3776	GTGGGGGG GGCTAGCTACAACGA AATATGTC	8573
3128	UGCCCCCC A CCGACUUU	3777	AAAGTCGG GGCTAGCTACAACGA GGGGGGCA	8574
3124	CCCCACCG A CUUCCGC	3778	GCGGAAAG GGCTAGCTACAACGA CGGTGGGG	8575
3117	GACUUUCC G CACCAAAA	3779	TTTTGGTG GGCTAGCTACAACGA GGAAAGTC	8576
3115	CUUCCGC A CCAAAAU	3780	CATTTTGG GGCTAGCTACAACGA GCGGAAAG	8577
3109	GCACCAA A UGCAUUA	3781	TGAATGCA GGCTAGCTACAACGA TTTGGTGC	8578
3107	ACCAAAU G CAUUCACG	3782	CGTGAATG GGCTAGCTACAACGA ATTTTGGT	8579
3105	CAAAUUG A UUCACGGA	3783	TCCGTGAA GGCTAGCTACAACGA GCATTTTG	8580
3101	AUGCAUUC A CGGAUGAC	3784	GTCATCCG GGCTAGCTACAACGA GAATGCAT	8581
3097	AUUCACGG A UGACCCCU	3785	AGGGGTCA GGCTAGCTACAACGA CCGTGAAT	8582
3094	CACGGAUG A CCCCUGA	3786	TCAAGGGG GGCTAGCTACAACGA CATCCGTG	8583
3085	CCCCUUG A CCCGCACA	3787	TGTGCGGG GGCTAGCTACAACGA TCAAGGGG	8584
3081	UUGAGCCC G CACAAGU	3788	ACTTTGTG GGCTAGCTACAACGA GGGCTCAA	8585
3079	GAGCCCGC A CAAAGUCC	3789	GGACTTTG GGCTAGCTACAACGA GCGGGCTC	8586
3074	CGCACAAA G UCCGGCAC	3790	GTGCGGGA GGCTAGCTACAACGA TTTGTGCG	8587
3069	AAAGUCCG G CACUUUUG	3791	CAAAAGTG GGCTAGCTACAACGA CGGACTTT	8588
3067	AGUCCGGC A CUUUUGCU	3792	AGCAAAAG GGCTAGCTACAACGA GCCGGACT	8589
3061	GCACUUUU G CUAUACCA	3793	TGGTATAG GGCTAGCTACAACGA AAAAGTGC	8590
3058	CUUUUGCU A UACCAGCC	3794	GGCTGGTA GGCTAGCTACAACGA AGCAAAAG	8591
3056	UUUGCUAU A CCAGCCUG	3795	CAGGCTGG GGCTAGCTACAACGA ATAGCAA	8592
3052	CUAUACCA G CCUGGAGC	3796	GCTCCAGG GGCTAGCTACAACGA TGGTATAG	8593
3045	AGCCUGGA G CACCAUGA	3797	TCATGGTG GGCTAGCTACAACGA TCCAGGCT	8594
3043	CCUGGAGC A CCAUGAGC	3798	GCTCATGG GGCTAGCTACAACGA GCTCCAGG	8595
3040	GGAGCACC A UGAGCGGG	3799	CCCGTCA GGCTAGCTACAACGA GGTGCTCC	8596
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2984	AGCUCUGG G UGGACCAC	3813	GTGGTCCA GGCTAGCTACAACGA CCAGAGCT	8610
2980	CUGGGUGG A CCACACAC	3814	GTGTGTGG GGCTAGCTACAACGA CCACCCAG	8611
2977	GGUGGACC A CACACGUG	3815	CACGTGTG GGCTAGCTACAACGA GGTCCACC	8612
2975	UGGACCAC A CACGUGAG	3816	CTCACGTG GGCTAGCTACAACGA GTGGTCCA	8613
2973	GACCACAC A CGUGAGGA	3817	TCCTCACG GGCTAGCTACAACGA GTGTGGTC	8614
2971	CCACACAC G UGAGGAGA	3818	TCTCCTCA GGCTAGCTACAACGA GTGTGTGG	8615
2962	UGAGGAGA A UGAUGGCA	3819	TGCCATCA GGCTAGCTACAACGA TCTCCTCA	8616
2959	GGAGAAUG A UGGACCG	3820	CGGTGCCA GGCTAGCTACAACGA CATTCTCC	8617
2956	GAAUGAUG G CACCGCGC	3821	GCGCGGTG GGCTAGCTACAACGA CATCATTC	8618
2954	AUGAUGGC A CCGCGCCC	3822	GGGCGCGG GGCTAGCTACAACGA GCCATCAT	8619
2951	AUGGCACC G CGCCCCC	3823	GGGGGCGG GGCTAGCTACAACGA GGTGCCAT	8620
2949	GGCACCGC G CCCCCC	3824	GGGGGGGG GGCTAGCTACAACGA GCGGTGCC	8621
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2923	GGGGGGGG A UCCACACU	3827	AGTGTGGA GGCTAGCTACAACGA CCCCCC	8624
2919	GGGGAUCC A CACUUGCA	3828	TGCAAGTG GGCTAGCTACAACGA GGATCCCC	8625
2917	GGAUCCAC A CUUGCAAC	3829	GTTGCAAG GGCTAGCTACAACGA GTGGATCC	8626
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2907	UUGCAACU G CGCCUCGG	3832	CCGAGGCG GGCTAGCTACAACGA AGTTGCAA	8629
2905	GCAACUGC G CCUCGGCU	3833	AGCCGAGG GGCTAGCTACAACGA GCAGTTGC	8630
2899	GCGCCUCG G CUCUGGUG	3834	CACCAGAG GGCTAGCTACAACGA CGAGGCGC	8631
2893	CGGCUCUG G UGAUAAGG	3835	CCTTATCA GGCTAGCTACAACGA CAGAGCCG	8632
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2883	GAUAAGGU A UUGCAACC	3838	GGTTGCAA GGCTAGCTACAACGA ACCTTATC	8635
2880	AAGGUAAU G CAACCACC	3839	GGTGGTTG GGCTAGCTACAACGA AATACCTT	8636
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2874	UUGCAACC A CCAUAUGA	3841	TCATATGG GGCTAGCTACAACGA GGTGCAA	8638
2871	CAACCACC A UAUGAGCC	3842	GGCTCATA GGCTAGCTACAACGA GGTGGTTG	8639
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2851	CGAGGAAC A CUUUGUAG	3847	CTACAAAG GGCTAGCTACAACGA GTTCTCG	8644
2846	AACACUUU G UAGUAUGG	3848	CCATACTA GGCTAGCTACAACGA AAAGTGTT	8645
2843	ACUUUGUA G UAUGGUGA	3849	TCACCATA GGCTAGCTACAACGA TACAAAGT	8646
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2835	GUAUGGUG A CAAGGUCA	3852	TGACCTTG GGCTAGCTACAACGA CACCATAC	8649
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2821	UCAAGAGU G CUAGACCU	3855	AGGTCTAG GGCTAGCTACAACGA ACTCTTGA	8652
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2806	CUACAAAA A CCACGCCU	3858	AGGCGTGG GGCTAGCTACAACGA TTTTGTAG	8655
2803	CAAAAACC A CGCCUCCG	3859	CGGAGGCG GGCTAGCTACAACGA GGTTTTTG	8656
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2793	GCCUCCGC A CGAUGCGG	3862	CCGCATCG GGCTAGCTACAACGA GCGGAGGC	8659
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2770	CCCGGUCC A UGGCGUAC	3868	GTACGCCA GGCTAGCTACAACGA GGACCGGG	8665

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2765	UCCAUGGC G UACGCCCC	3870	CGGGCGTA GGCTAGCTACAACGA GCCATGGA	8667
2763	CAUGGCGU A CGCCCGUG	3871	CACGGGCG GGCTAGCTACAACGA ACGCCATG	8668
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2757	GUACGCCC G UGGUGGUA	3873	TACCACCA GGCTAGCTACAACGA GGGCGTAC	8670
2754	CGCCCGUG G UGUUAACG	3874	CGTTACCA GGCTAGCTACAACGA CACGGGCG	8671
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2046	GAUGUUGC A CGGGGGGC	4050	GCCCCCGG GGCTAGCTACAACGA GCAACATC	8847
2039	CACGGGGG G CCCCCGCA	4051	TGCGGGGG GGCTAGCTACAACGA CCCCCGTG	8848
2033	GGGCCCC G CACGUCU	4052	AAGACGTG GGCTAGCTACAACGA GGGGGCCC	8849
2031	GCCCCCG A CGUCUUGG	4053	CCAAGACG GGCTAGCTACAACGA GCGGGGGC	8850
2029	CCCCGCAC G UCUUGGUG	4054	CACCAAGA GGCTAGCTACAACGA GTGCGGGG	8851
2023	ACGUCUUG G UGAACCCA	4055	TGGGTTCA GGCTAGCTACAACGA CAAGACGT	8852
2019	CUUGGUGA A CCCAGUGC	4056	GCACTGGG GGCTAGCTACAACGA TCACCAAG	8853
2014	UGAACCCA G UGCCAUUC	4057	GAATGGCA GGCTAGCTACAACGA TGGGTTCA	8854
2012	AACCCAGU G CCAUUCAU	4058	ATGAATGG GGCTAGCTACAACGA ACTGGGTT	8855
2009	CCAGUGCC A UUCAUCCA	4059	TGGATGAA GGCTAGCTACAACGA GCACTGG	8856
2005	UGCCAUUC A UCCAUGUG	4060	CACATGGA GGCTAGCTACAACGA GAATGGCA	8857
2001	AUUCAUCC A UGUGCAGC	4061	GCTGCACA GGCTAGCTACAACGA GGATGAAT	8858
1999	UCAUCCAU G UGCAGCCG	4062	CGGTGCA GGCTAGCTACAACGA ATGGATGA	8859
1997	AUCCAUGU G CAGCCGAA	4063	TTCGGCTG GGCTAGCTACAACGA ACATGGAT	8860
1994	CAUGUGCA G CCGAACCA	4064	TGGTTCGG GGCTAGCTACAACGA TGCACATG	8861
1989	GCAGCCGA A CCAGUUGC	4065	GCAACTGG GGCTAGCTACAACGA TCGGCTGC	8862
1985	CCGAACCA G UUGCCUUG	4066	CAAGGCAA GGCTAGCTACAACGA TGGTTCGG	8863
1982	AACCAGUU G CCUUGCGG	4067	CCGCAAGG GGCTAGCTACAACGA AACTGGTT	8864
1977	GUUGCCUU G CGGCGGCC	4068	GGCCGCCG GGCTAGCTACAACGA AAGGCAAC	8865
1974	GCCUUGCG G CGGCCCG	4069	CGCGGCCG GGCTAGCTACAACGA CGCAAGGC	8866
1971	UUGCGGCG G CCGCGUGU	4070	ACACGCGG GGCTAGCTACAACGA CGCCGCAA	8867
1968	CGGCGGCC G CGUGUUGU	4071	ACAACACG GGCTAGCTACAACGA GCGGCCCG	8868
1966	GCGGCCCG G UGUUUGU	4072	CAACAACA GGCTAGCTACAACGA ACGCCGCG	8869
1964	GGCCGCGU G UUGUUGAG	4073	CTCAACAA GGCTAGCTACAACGA ACGCGGCC	8870
1961	CGCGUGUU G UUGAGGAG	4074	CTCCTCAA GGCTAGCTACAACGA AACACGCG	8871
1953	GUUGAGGA G CAGCACGU	4075	ACGTGCTG GGCTAGCTACAACGA TCCTCAAC	8872
1950	GAGGAGCA G CACGUCCG	4076	CGGACGTG GGCTAGCTACAACGA TGCTCTC	8873
1948	GGAGCAGC A CGUCCGUC	4077	GACGGACG GGCTAGCTACAACGA GCTGCTCC	8874
1946	AGCAGCAC G UCCGUCUC	4078	GAGACGGA GGCTAGCTACAACGA GTGCTGCT	8875
1942	GCACGUCC G UCUCGUUC	4079	GAACGAGA GGCTAGCTACAACGA GGACGTGC	8876
1937	UCCGUCUC G UUCGCCCC	4080	GGGGCGAA GGCTAGCTACAACGA GAGACGGA	8877
1933	UCUCGUUC G CCCCCCAG	4081	CTGGGGGG GGCTAGCTACAACGA GAACGAGA	8878
1925	GCCCCCA G UUAUACGU	4082	ACGTATAA GGCTAGCTACAACGA TGGGGGGC	8879
1922	CCCCAGUU A UACGUGGG	4083	CCCACGTA GGCTAGCTACAACGA AACTGGGG	8880
1920	CCAGUUAU A CGUGGGGG	4084	CCCCACG GGCTAGCTACAACGA ATAACCTG	8881
1918	AGUUAUAC G UGGGGGCG	4085	CGCCCCCA GGCTAGCTACAACGA GTATAACT	8882
1912	ACGUGGGG G CGCCGAAA	4086	TTTCGGCG GGCTAGCTACAACGA CCCCACGT	8883
1910	GUGGGGGC G CCGAAACG	4087	CGTTCGGG GGCTAGCTACAACGA GCCCCCAC	8884
1904	GCGCCGAA A CGGUCGGU	4088	ACCACCGG GGCTAGCTACAACGA TTCGGCGC	8885
1901	CCGAAACG G UCGGUCGU	4089	ACGACCGA GGCTAGCTACAACGA CGTTTCGG	8886
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1894	GGUCGGUC G UCCCCACC	4091	GGTGGGGA GGCTAGCTACAACGA GACCGACC	8888
1888	UCGUCCCC A CCACAACA	4092	TGTTGTGG GGCTAGCTACAACGA GGGGACGA	8889
1885	UCCCCACC A CAACAGGG	4093	CCCTGTTG GGCTAGCTACAACGA GGTGGGGA	8890
1882	CCACCACA A CAGGCUU	4094	AAGCCCTG GGCTAGCTACAACGA TGTGGTGG	8891
1877	ACAACAGG G CUUGGGGU	4095	ACCCCAAG GGCTAGCTACAACGA CCTGTTGT	8892
1870	GGCUUGGG G UGAAGCAA	4096	TTGCTTCA GGCTAGCTACAACGA CCCAAGCC	8893

1865	GGGGUGAA G CAAUACAC	4097	GTGTATTG GGCTAGCTACAACGA TTCACCCC	8894
1862	GUGAAGCA A UACACUGG	4098	CCAGTGTA GGCTAGCTACAACGA TGCTTCAC	8895
1860	GAAGCAAU A CACUGGAC	4099	GTCCAGTG GGCTAGCTACAACGA ATTGCTTC	8896
1858	AGCAUAUAC A CUGGACCA	4100	TGGTCCAG GGCTAGCTACAACGA GTATTGCT	8897
1853	UACACUGG A CCACAUAC	4101	GTATGTGG GGCTAGCTACAACGA CCAGTGTA	8898
1850	ACUGGACC A CAUACCUG	4102	CAGGTATG GGCTAGCTACAACGA GGTCCAGT	8899
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1842	ACAUACCU G CGAUGCGG	4105	CCGCATCG GGCTAGCTACAACGA AGGTATGT	8902
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1826	GGUACGAU A CCACACGG	4111	CCGTGTGG GGCTAGCTACAACGA ATCGTACC	8908
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1821	GAUACCAC A CGGCCGCG	4113	CGCGGCCG GGCTAGCTACAACGA GTGGTATC	8910
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1815	ACACGGCC G CGGUGCGU	4115	ACGCACCG GGCTAGCTACAACGA GGCCGTGT	8912
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1808	CGCGGUGC G UAGUGCCA	4118	TGGCACTA GGCTAGCTACAACGA GCACCGCG	8915
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1796	UGCCAGCA A UAGGGCCU	4122	AGGCCCTA GGCTAGCTACAACGA TGCTGGCA	8919
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1765	GGCCCUCG G UGUAGGUG	4128	CACCTACA GGCTAGCTACAACGA CGAGGGCC	8925
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1751	GUGAUAGG A CCCCACCC	4132	GGGTGGGG GGCTAGCTACAACGA CCTATCAC	8929
1746	AGGACCCC A CCCUGAG	4133	CTCAGGGG GGCTAGCTACAACGA GGGGTCTT	8930
1738	ACCCUGA G CGAACUUG	4134	CAAGTTCG GGCTAGCTACAACGA TCAGGGGT	8931
1734	CUGAGCGA A CUUGUCAA	4135	TTGACAAAG GGCTAGCTACAACGA TCGCTCAG	8932
1730	GCGAACUU G UCAAUGGA	4136	TCCATTGA GGCTAGCTACAACGA AAGTTCGC	8933
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1721	UCAAUGGA G CGGCAGCU	4138	AGCTGCCG GGCTAGCTACAACGA TCCATTGA	8935
1718	AUGGAGCG G CAGCUGGC	4139	GCCAGCTG GGCTAGCTACAACGA CGCTCCAT	8936
1715	GAGCGGCA G CUGGCCAA	4140	TTGGCCAG GGCTAGCTACAACGA TGCCGCTC	8937
1711	GGCAGCUG G CCAAGCGC	4141	GCGCTTGG GGCTAGCTACAACGA CAGCTGCC	8938
1706	CUGGCCAA G CGCUGUGG	4142	CCACAGCG GGCTAGCTACAACGA TTGGCCAG	8939
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1701	CAAGCGCU G UGGGCAUC	4144	GATGCCCA GGCTAGCTACAACGA AGCGCTTG	8941
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1685	CCGGACGA G UUGAACCU	4148	AGGTTCAA GGCTAGCTACAACGA TCGTCCGG	8945
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1672	ACCUGUGU G CAUAGAAC	4152	GTTCTATG GGCTAGCTACAACGA ACACAGGT	8949
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1662	AUAGAACA G UGCAGCAA	4155	TTGCTGCA GGCTAGCTACAACGA TGTTCAT	8952
1660	AGAACAGU G CAGCAAUG	4156	CATTGCTG GGCTAGCTACAACGA ACTGTTCT	8953
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1654	GUGCAGCA A UGAACCCG	4158	CGGGTTCA GGCTAGCTACAACGA TGCTGCAC	8955
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1192	CGAGGAAG A CAGAUCCG	4273	CGGATCTG GGCTAGCTACAACGA CTTCTCTG	9070
1188	GAAGACAG A UCCGCAGA	4274	TCTGCGGA GGCTAGCTACAACGA CTGTCTTC	9071
1184	ACAGAUCC G CAGAGAUC	4275	GATCTCTG GGCTAGCTACAACGA GGATCTGT	9072
1178	CCGCAGAG A UCCCCAC	4276	GTGGGGGA GGCTAGCTACAACGA CTCTGCCG	9073
1171	GAUCCCC A CGUACUA	4277	TATGTACG GGCTAGCTACAACGA GGGGGATC	9074
1169	UCCCCAC G UACAUAGC	4278	GCTATGTA GGCTAGCTACAACGA GTGGGGGA	9075
1167	CCCCACGU A CAUAGCAG	4279	CTGTATAG GGCTAGCTACAACGA ACGTGGGG	9076
1165	CCACGUAC A UAGCAGAG	4280	CTCTGCTA GGCTAGCTACAACGA GTACGTGG	9077
1162	CGUACUA G CAGAGCAG	4281	CTGTCTG GGCTAGCTACAACGA TATGTACG	9078
1157	AUAGCAGA G CAGAAAGC	4282	GCTTCTG GGCTAGCTACAACGA TCTGTAT	9079
1150	AGCAGAAA G CAGCCGCC	4283	GGCGGCTG GGCTAGCTACAACGA TTTCTGCT	9080
1147	AGAAAGCA G CCGCCCCA	4284	TGGGGCGG GGCTAGCTACAACGA TGCTTTCT	9081
1144	AAGCAGCC G CCCAACG	4285	CGTTGGGG GGCTAGCTACAACGA GGCTGCTT	9082
1138	CCGCCCCA A CGAGCAA	4286	TTTGCTCG GGCTAGCTACAACGA TGGGGCGG	9083
1134	CCCAACGA G CAAUUCGA	4287	TCGATTTG GGCTAGCTACAACGA TCGTTGGG	9084
1130	ACGAGCAA A UCGACGUG	4288	CACGTCGA GGCTAGCTACAACGA TTGCTCGT	9085
1126	GCAAUUCG A CGUGACGC	4289	GCGTCACG GGCTAGCTACAACGA CGATTTGC	9086
1124	AAAUUCGAC G UGACGCCG	4290	CGGCGTCA GGCTAGCTACAACGA GTCGATTT	9087
1121	UCGACGUG A CGCCGUU	4291	ATACGGCG GGCTAGCTACAACGA CACGTCGA	9088
1119	GACGUGAC G CCGUAUCG	4292	CGATACGG GGCTAGCTACAACGA GTCACGTC	9089
1116	GUGACGCC G UAUCGUCG	4293	CGACGATA GGCTAGCTACAACGA GGCGTCAC	9090
1114	GACGCCGU A UCGUCGUA	4294	TACGACGA GGCTAGCTACAACGA ACGGCGTC	9091
1111	GCCGUUUC G UCGUAGUG	4295	CACTACGA GGCTAGCTACAACGA GATACGGC	9092
1108	GUAUCGUC G UAGUGGGG	4296	CCCCACTA GGCTAGCTACAACGA GACGATAC	9093
1105	UCGUCGUA G UGGGGAUG	4297	CATCCCCA GGCTAGCTACAACGA TACGACGA	9094
1099	UAGUGGGG A UGCUGGCA	4298	TGCCAGCA GGCTAGCTACAACGA CCCCCACTA	9095
1097	GUGGGGAU G CUGGCAU	4299	AATGCCAG GGCTAGCTACAACGA ATCCCCAC	9096
1093	GGAUGCUG G CAUUCUG	4300	CAGGAATG GGCTAGCTACAACGA CAGCATCC	9097
1091	AUGCUGG A UUCCUGG	4301	GCCAGGAA GGCTAGCTACAACGA GCCAGCAT	9098
1084	CAUUCUG G CCGCAGC	4302	GCTCGCGG GGCTAGCTACAACGA CAGGAATG	9099
1081	UCCUGGCC G CGAGCGUG	4303	CACGCTCG GGCTAGCTACAACGA GGCCAGGA	9100
1077	GGCCGCGA G CGUGGGAG	4304	CTCCACG GGCTAGCTACAACGA TCGCGGCC	9101
1075	CCGCGAGC G UGGGAGUG	4305	CACTCCCA GGCTAGCTACAACGA CTCGCGG	9102
1069	GCGUGGGA G UGAGCGCU	4306	AGCGCTCA GGCTAGCTACAACGA TCCCACGC	9103
1065	GGGAGUGA G CGCUACCC	4307	GGGTAGCG GGCTAGCTACAACGA TCACTCCC	9104
1063	GAGUGAGC G CUACCCAG	4308	CTGGGTAG GGCTAGCTACAACGA GCTCACTC	9105
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1055	GCUACCCA G CAGCGGGA	4310	TCCCGCTG GGCTAGCTACAACGA TGGGTAGC	9107
1052	ACCCAGCA G CGGGAGGA	4311	TCCTCCCG GGCTAGCTACAACGA TGCTGGGT	9108
1043	CGGGAGGA G UUGUUCUC	4312	GAGAACAA GGCTAGCTACAACGA TCCTCCCG	9109
1040	GAGGAGUU G UUCUCCG	4313	CGGGAGAA GGCTAGCTACAACGA AACTCCTC	9110
1030	UCUCCCGA A CGCAGGGC	4314	GCCCTGCG GGCTAGCTACAACGA TCGGGAGA	9111
1028	UCCCGAAC G CAGGGCAC	4315	GTGCCCTG GGCTAGCTACAACGA GTTCGGGA	9112
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1021	CGCAGGGC A CGCACCCC	4317	GGGTGCGG GGCTAGCTACAACGA GCCCTGCG	9114
1019	CAGGGCAC G CACCCCGG	4318	CCGGGGTG GGCTAGCTACAACGA GTGCCCTG	9115
1017	GGGCACGC A CCCCAGGG	4319	CCCCGGGG GGCTAGCTACAACGA GCGTGCCC	9116
1009	ACCCCGGG G UGUGCAUG	4320	CATGCACA GGCTAGCTACAACGA CCCGGGGT	9117
1007	CCCGGGGU G UGCAUGAU	4321	ATCATGCA GGCTAGCTACAACGA ACCCCGGG	9118
1005	CGGGGUGU G CAUGAUCA	4322	TGATCATG GGCTAGCTACAACGA ACACCCCG	9119
1003	GGGUGUGC A UGAUCAUG	4323	CATGATCA GGCTAGCTACAACGA GCACACCC	9120
1000	UGUGCAUG A UCAUGUCC	4324	GGACATGA GGCTAGCTACAACGA CATGCACA	9121

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995	AUGAUCAU G UCCUCUGC	4326	GCAGAGGA GGCTAGCTACAACGA ATGATCAT	9123
988	UGUCCUCU G CCUCAUAC	4327	GTATGAGG GGCTAGCTACAACGA AGAGGACA	9124
983	UCUGCCUC A UACACAAU	4328	ATTGTGTA GGCTAGCTACAACGA GAGGCAGA	9125
981	UGCCUCAU A CACAAUGC	4329	GCATTGTG GGCTAGCTACAACGA ATGAGGCA	9126
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974	UACACAAU G CUUGAGUU	4332	AACTCAAG GGCTAGCTACAACGA ATTGTGTA	9129
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962	GAGUUGGA G CAAUCGUU	4334	AACGATTG GGCTAGCTACAACGA TCCAACCTC	9131
959	UUGGAGCA A UCGUUCGU	4335	ACGAACGA GGCTAGCTACAACGA TGCTCCAA	9132
956	GAGCAAUC G UUCGUGAC	4336	GTCACGAA GGCTAGCTACAACGA GATTGCTC	9133
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947	UUCGUGAC A UGGUACAG	4339	CTGTACCA GGCTAGCTACAACGA GTCACGAA	9136
944	GUGACAUG G UACAGCCC	4340	GGGCTGTA GGCTAGCTACAACGA CATGTGTC	9137
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939	AUGGUACA G CCCGGACG	4342	CGTCCGGG GGCTAGCTACAACGA TGTACCAT	9139
933	CAGCCCGG A CGCGUUGC	4343	GCAACGCG GGCTAGCTACAACGA CCGGGCTG	9140
931	GCCCGGAC G CGUUGCAC	4344	GTGCAACG GGCTAGCTACAACGA GTCCGGGC	9141
929	CCGGACGC G UUGCACAC	4345	GTGTGCAA GGCTAGCTACAACGA GCGTCCGG	9142
926	GACGCGUU G CACACCUC	4346	GAGGTGTG GGCTAGCTACAACGA AACCGGTC	9143
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922	CGUUGCAC A CCUCAUAA	4348	TTATGAGG GGCTAGCTACAACGA GTGCAACG	9145
917	CACACCUC A UAAGCGGA	4349	TCCGCTTA GGCTAGCTACAACGA GAGGTGTG	9146
913	CCUCAUAA G CGGAGGCU	4350	AGCCTCCG GGCTAGCTACAACGA TTATGAGG	9147
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901	AGGCUGGG A UGGUCAGA	4352	TCTGACCA GGCTAGCTACAACGA CCCAGCCT	9149
898	CUGGGAUG G UCAGACAG	4353	CTGTCTGA GGCTAGCTACAACGA CATCCCAG	9150
893	AUGGUCAG A CAGGGCAG	4354	CTGCCCTG GGCTAGCTACAACGA CTGACCAT	9151
888	CAGACAGG G CAGCAGAG	4355	CTCTGCTG GGCTAGCTACAACGA CCTGTCTG	9152
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713	GUGAGGGU A UCGAUGAC	4395	GTCATCGA GGCTAGCTACAACGA ACCCTCAC	9192
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389	GGGCGGCG G UUGGUGUU	4468	AACACCAA GGCTAGCTACAACGA CGCCGCC	9265
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269	CUUUCGCG A CCCAACAC	4497	GTGTTGGG GGCTAGCTACAACGA CGCGAAAG	9294
264	GCGACCCA A CACUACUC	4498	GAGTAGTG GGCTAGCTACAACGA TGGGTCGC	9295
262	GACCCAAC A CUACUCGG	4499	CCGAGTAG GGCTAGCTACAACGA GTTGGGTC	9296
259	CCAACACU A CUCGGCUA	4500	TAGCCGAG GGCTAGCTACAACGA AGTGTGTTG	9297
254	ACUACUCG G CUAGCAGU	4501	ACTGCTAG GGCTAGCTACAACGA CGAGTAGT	9298
250	CUCGGCUA G CAGUCUCG	4502	CGAGACTG GGCTAGCTACAACGA TAGCCGAG	9299
247	GGCUAGCA G UCUCGCGG	4503	CCGCGAGA GGCTAGCTACAACGA TGCTAGCC	9300
242	GCAGUCUC G CGGGGGCA	4504	TGCCCCCG GGCTAGCTACAACGA GAGACTGC	9301
236	UCGCGGGG G CACGCCCA	4505	TGGGCGTG GGCTAGCTACAACGA CCCCCGCA	9302
234	GCGGGGGG A CGCCCAA	4506	TTTGGGCG GGCTAGCTACAACGA GCCCCGCG	9303
232	GGGGGCGAC G CCCAAAU	4507	GATTTGGG GGCTAGCTACAACGA GTGCCCCC	9304
226	ACGCCCAA A UCUCAGG	4508	CCTGGAGA GGCTAGCTACAACGA TTGGGCGT	9305
218	AUCUCCAG G CAUUGAGC	4509	GCTCAATG GGCTAGCTACAACGA CTGGAGAT	9306
216	CUCCAGGC A UUGAGCGG	4510	CCGCTCAA GGCTAGCTACAACGA GCCTGGAG	9307
211	GGCAUUGA G CGGGUUGA	4511	TCAACCCG GGCTAGCTACAACGA TCAATGCC	9308
207	UUGAGCGG G UUGAUCCA	4512	TGGATCAA GGCTAGCTACAACGA CCGCTCAA	9309
203	GCGGGUUG A UCCAAGAA	4513	TTCTTGGA GGCTAGCTACAACGA CAACCCGC	9310
191	AAGAAAGG A CCCGUCG	4514	CGACCGGG GGCTAGCTACAACGA CCTTTCTT	9311
186	AGGACCCG G UCGUCCUG	4515	CAGGACGA GGCTAGCTACAACGA CGGGTCCT	9312
183	ACCCGGUC G UCCUGGCA	4516	TGCCAGGA GGCTAGCTACAACGA GACCGGGT	9313
177	UCGUCCUG G CAAUUCCG	4517	CGGAATTG GGCTAGCTACAACGA CAGGACGA	9314
174	UCCUGGCA A UCCGGUG	4518	CACCGGAA GGCTAGCTACAACGA TGCCAGGA	9315
168	CAAUUCCG G UGUACUCA	4519	TGAGTACA GGCTAGCTACAACGA CGGAATTG	9316
166	AUUCCGGU G UACUCACC	4520	GGTGAGTA GGCTAGCTACAACGA ACCGGAAT	9317
164	UCCGGUGU A CUCACCGG	4521	CCGGTGAG GGCTAGCTACAACGA ACACCGGA	9318
160	GUGUACUC A CCGGUUCC	4522	GGAACCGG GGCTAGCTACAACGA GAGTACAC	9319
156	ACUCACCG G UUCGCGAG	4523	CTGCGGAA GGCTAGCTACAACGA CGGTGAGT	9320
151	CCGGUUCG G CAGACCAC	4524	GTGGTCTG GGCTAGCTACAACGA GGAACCGG	9321
147	UUCGCGAG A CCACUAUG	4525	CATAGTGG GGCTAGCTACAACGA CTGCGGAA	9322
144	CGCAGACC A CUAUGGCU	4526	AGCCATAG GGCTAGCTACAACGA GGTCTGCG	9323
141	AGACCACA A UGGCUCUC	4527	GAGAGCCA GGCTAGCTACAACGA AGTGGTCT	9324
138	CCACUAUG G CUCUCCCG	4528	CGGGAGAG GGCTAGCTACAACGA CATGTGGG	9325
120	GAGGGGGG G UCCUGGAG	4529	CTCCAGGA GGCTAGCTACAACGA CCCCCCTC	9326
111	UCCUGGAG G CUGCACGA	4530	TCGTGCAG GGCTAGCTACAACGA CTCCAGGA	9327
108	UGGAGGCU G CACGACAC	4531	GTGTCGTG GGCTAGCTACAACGA AGCCTCCA	9328
106	GAGGCUGC A CGACACUC	4532	GAGTGTCT GGCTAGCTACAACGA GCAGCTCT	9329
103	GCUGCACG A CACUCAUA	4533	TATGAGTG GGCTAGCTACAACGA CGTGCAGC	9330
101	UGCACGAC A CUCUAUCU	4534	AGTATGAG GGCTAGCTACAACGA GTCGTGCA	9331
97	CGACACUC A UACUAACG	4535	CGTTAGTA GGCTAGCTACAACGA GAGTGTCT	9332
95	ACACUCAU A CUAACGCC	4536	GGCGTTAG GGCTAGCTACAACGA ATGAGTGT	9333
91	UCAUACUA A CGCCAUGG	4537	CCATGGCG GGCTAGCTACAACGA TAGTATGA	9334
89	AUACUAAC G CCAUGGCU	4538	AGCCATGG GGCTAGCTACAACGA GTTAGTAT	9335
86	CUAACGCC A UGGCUAGA	4539	TCTAGCCA GGCTAGCTACAACGA GGCCTTAG	9336
83	ACGCCAUG G CUAGACGC	4540	GCGTCTAG GGCTAGCTACAACGA CATGGCGT	9337
78	AUGGCUAG A CGCUUUCU	4541	AGAAAGCG GGCTAGCTACAACGA CTAGCCAT	9338
76	GGCUAGAC G CUUUCUGC	4542	GCAGAAAG GGCTAGCTACAACGA GTCTAGCC	9339
69	CGCUUUCU G CGUGAAGA	4543	TCTTCACG GGCTAGCTACAACGA AGAAAGCG	9340
67	CUUUCUGC G UGAAGACA	4544	TGTCTTCA GGCTAGCTACAACGA GCAGAAAG	9341
61	GCGUGAAG A CAGUAGUU	4545	AACTACTG GGCTAGCTACAACGA CTTACCGC	9342
58	UGAAGACA G UAGUCCU	4546	AGGAACTA GGCTAGCTACAACGA TGTCTTCA	9343
55	AGACAGUA G UUCUCAC	4547	GTGAGGAA GGCTAGCTACAACGA TACTGTCT	9344
48	AGUUCUC A CAGGGGAG	4548	CTCCCCTG GGCTAGCTACAACGA GAGGAACT	9345
40	ACAGGGGA G UGAUCUAU	4549	ATAGATCA GGCTAGCTACAACGA TCCCCTGT	9346
37	GGGAGUG A UCUAUGGU	4550	ACCATAGA GGCTAGCTACAACGA CACTCCCC	9347
33	AGUAGUCU A UGGUGGAG	4551	CTCCACCA GGCTAGCTACAACGA AGATCACT	9348
30	GAUCUAUG G UGGAGUGU	4552	ACACTCCA GGCTAGCTACAACGA CATAGATC	9349

25	AUGGUGGA G UGUCGCCC	4553	GGGCGACA GGCTAGCTACAACGA TCCACCAT	9350
23	GGUGGAGU G UCGCCCCC	4554	GGGGGCGA GGCTAGCTACAACGA ACTCCACC	9351

Input Sequence = HPCK1S1. Cut Site = R/Y

Arm Length = 8. Core Sequence = GGCTAGCTACAACGA

HPCK1S1 Hepatitis C virus (strain HCV-1b, clone HCV-K1-S1), complete genome; acc#
gi|1030702|dbj|D50483.1; 9410 nt

Table V: Synthetic anti-HCV nucleic acid molecule and Target Sequences

ref pos	Ref Seq	Target	Seq ID	RPI#	Nucleic Acid	Seq ID	Nucleic Acid Alias
195	HCV+	GGGUCCU U UCUUGGA	4556	15364	c ₅ c ₅ s ₅ a ₅ s ₅ ga cUGAuGaggcgaaagccGaa Aggacc B	9352	Hammerhead
342	HCV+	AGACCGUGCAUCAUGAGCAC	4555	17501	G ₅ T ₅ G ₅ C ₅ T ₅ C ₅ A ₅ T ₅ G ₅ A ₅ T ₅ G ₅ C ₅ A ₅ C ₅ G ₅ T ₅ C ₅ T	9353	Antisense
195	HCV+	GGGUCCU U UCUUGGA	4556	17558	c ₅ s ₅ a ₅ s ₅ ga cUGAuGaggcguaagccGaz Aggacc B	9354	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	17559	c ₅ s ₅ a ₅ s ₅ ga cUGAuGaggcguaagccGaa AggaZc B	9355	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	17560	Z ₅ c ₅ s ₅ a ₅ s ₅ ga cUGAuGaggcguaagccGaa Aggacc B	9356	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	17561	Z c ₅ a ₅ s ₅ ga cUGAuGaggcguaagccGaa Aggacc B	9357	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	18012	ccaaga cUGAuGaggcguaagccGaa Aggacc B	9358	Hammerhead
82	HCV+	GGGUCUA G CCAUGGC	4557	18744	g ₅ c ₅ s ₅ a ₅ s ₅ ugg GccgaagGCGaGucaaGGuCu uagagc B	9359	Zinzyme
100	HCV+	AGUAUGA G UGUCGUG	4558	18745	c ₅ a ₅ c ₅ s ₅ aca GccgaagGCGaGucaaGGuCu ucauacu B	9360	Zinzyme
102	HCV+	UAUGAGU G UCGUGCA	4559	18746	u ₅ g ₅ c ₅ a ₅ s ₅ ga GccgaagGCGaGucaaGGuCu acucaua B	9361	Zinzyme
105	HCV+	GAGUGUC G UGCAGCC	4560	18747	g ₅ g ₅ c ₅ u ₅ gca GccgaagGCGaGucaaGGuCu gacacuc B	9362	Zinzyme
107	HCV+	GUGUCGU G CAGCCUC	4561	18748	g ₅ a ₅ g ₅ g ₅ cug GccgaagGCGaGucaaGGuCu acgacac B	9363	Zinzyme
146	HCV+	CAUAGUG G UCUGCGG	4562	18749	c ₅ s ₅ g ₅ c ₅ aga GccgaagGCGaGucaaGGuCu cacuaug B	9364	Zinzyme
190	HCV+	CGACCGG G UCCUJUC	4563	18750	g ₅ a ₅ a ₅ s ₅ gga GccgaagGCGaGucaaGGuCu ccgguug B	9365	Zinzyme
217	HCV+	GCUCAU G CCUGGAG	4564	18751	c ₅ u ₅ c ₅ c ₅ agg GccgaagGCGaGucaaGGuCu auugagc B	9366	Zinzyme
231	HCV+	GAUUUGG G CGUGCCC	4565	18752	g ₅ g ₅ g ₅ c ₅ acg GccgaagGCGaGucaaGGuCu ccaaac B	9367	Zinzyme
258	HCV+	UAGCCGA G UAGUGUU	4566	18753	a ₅ a ₅ s ₅ a ₅ cua GccgaagGCGaGucaaGGuCu ucggcua B	9368	Zinzyme
307	HCV+	GGUGCUU G CGAGUGC	4567	18754	g ₅ c ₅ a ₅ c ₅ ucg GccgaagGCGaGucaaGGuCu aagcacc B	9369	Zinzyme
77	HCV+	GAAAGC G UCUAGC	4568	18755	g ₅ c ₅ u ₅ a ₅ ga GccgaagGCGaGucaaGGuCu gcuuuc B	9370	Zinzyme
77	HCV+	AGAAAGC G UCUAGCC	4569	18756	g ₅ g ₅ c ₅ u ₅ aga GccgaagGCGaGucaaGGuCu gcuuucu B	9371	Zinzyme
88	HCV+	AGCCAUG G CGUUAGU	4570	18757	a ₅ c ₅ u ₅ a ₅ acg GccgaagGCGaGucaaGGuCu cauggcu B	9372	Zinzyme
94	HCV+	GGCGUUA G UAUGAGU	4571	18758	a ₅ c ₅ u ₅ c ₅ aua GccgaagGCGaGucaaGGuCu uaagcc B	9373	Zinzyme
102	HCV+	AUGAGU G UCGUGC	4572	18759	g ₅ c ₅ a ₅ c ₅ ga GccgaagGCGaGucaaGGuCu acucau B	9374	Zinzyme
105	HCV+	AGUGUC G UGCAGC	4573	18760	g ₅ c ₅ u ₅ g ₅ ca GccgaagGCGaGucaaGGuCu gacacu B	9375	Zinzyme
110	HCV+	UCGUGCA G CCUCCAG	4574	18761	c ₅ u ₅ g ₅ g ₅ agg GccgaagGCGaGucaaGGuCu ugcaaga B	9376	Zinzyme
137	HCV+	GGGAGA G CCAUAG	4575	18762	c ₅ u ₅ a ₅ u ₅ gg GccgaagGCGaGucaaGGuCu ucucc B	9377	Zinzyme
137	HCV+	CGGGAGA G CCAUAGU	4576	18763	a ₅ c ₅ u ₅ a ₅ ugg GccgaagGCGaGucaaGGuCu ucucccg B	9378	Zinzyme
146	HCV+	AUAGUG G UCUGCG	4577	18764	c ₅ g ₅ c ₅ a ₅ ga GccgaagGCGaGucaaGGuCu cacua B	9379	Zinzyme
150	HCV+	GUGGUCU G CGGAACC	4578	18765	g ₅ g ₅ u ₅ u ₅ ccg GccgaagGCGaGucaaGGuCu agaccac B	9380	Zinzyme

167	HCV+	GAGUACACCGGAA	4684	22525	U ₅ U ₅ C ₅ C ₅ g ₅ g ₅ cUGAUgagccgcuuaggccGaa luacuc B	9486	Inozyme
139	HCV+	GAGAGCCAUAGUG	4685	22526	C ₅ a ₅ C ₅ U ₅ au cUGAUgagccgcuuaggccGaa lcucuc B	9487	Inozyme
140	HCV+	AGAGCCAUAGUGG	4686	22527	C ₅ C ₅ a ₅ C ₅ u ₅ cUGAUgagccgcuuaggccGaa lgcucu B	9488	Inozyme
281	HCV+	AAGGCCUUGUGGU	4687	22528	a ₅ C ₅ C ₅ a ₅ ca cUGAUgagccgcuuaggccGaa lgcucu B	9489	Inozyme
130	HCV+	CCCUCCCGGGAGA	4688	22529	U ₅ C ₅ U ₅ C ₅ cc cUGAUgagccgcuuaggccGaa lgaggg B	9490	Inozyme
280	HCV+	AAAGGCCUUGUGG	4689	22530	C ₅ C ₅ a ₅ C ₅ ca cUGAUgagccgcuuaggccGaa lccuuu B	9491	Inozyme
149	HCV+	GUGGUCUCGCGGAA	4690	22531	U ₅ U ₅ C ₅ C ₅ gc cUGAUgagccgcuuaggccGaa laccac B	9492	Inozyme
194	HCV+	GGGUCCUUCUUG	4691	22532	C ₅ a ₅ C ₅ U ₅ aa cUGAUgagccgcuuaggccGaa lgaccc B	9493	Inozyme
255	HCV+	GCUAGCCGAGUAG	4692	22533	C ₅ U ₅ a ₅ C ₅ uc cUGAUgagccgcuuaggccGaa lcuagc B	9494	Inozyme
294	HCV+	ACUGCCUGAUAGG	4693	22534	C ₅ C ₅ U ₅ a ₅ uc cUGAUgagccgcuuaggccGaa lgcagu B	9495	Inozyme
293	HCV+	UACUGCCUGAUAG	4694	22535	C ₅ U ₅ a ₅ U ₅ ca cUGAUgagccgcuuaggccGaa lcagua B	9496	Inozyme
290	HCV+	UGGUACUGCCUGA	4695	22536	U ₅ C ₅ a ₅ U ₅ gc cUGAUgagccgcuuaggccGaa luacca B	9497	Inozyme
169	HCV+	GUACACCGGAAU	4696	22537	a ₅ a ₅ U ₅ U ₅ cc cUGAUgagccgcuuaggccGaa luguac B	9498	Inozyme
293	HCV+	GUACUGCCUGAUAGG	4697	22544	C ₅ C ₅ U ₅ a ₅ uca cUGAUgagccgcuuaggccGaa lcaguac B	9499	Inozyme
294	HCV+	UACUGCCUGAUAGG	4698	22545	C ₅ C ₅ C ₅ U ₅ auc cUGAUgagccgcuuaggccGaa lgcagua B	9500	Inozyme
281	HCV+	AAAGGCCUUGUGGUA	4699	22546	U ₅ a ₅ C ₅ C ₅ aca cUGAUgagccgcuuaggccGaa lgcuuu B	9501	Inozyme
166	HCV+	UGAGUACACCGGA	4700	22549	U ₅ C ₅ C ₅ g ₅ g ₅ u cUGAUgagccgcuuaggccGaa Uacuca B	9502	Amberzyme
168	HCV+	AGUACACCGGAAU	4701	22550	a ₅ U ₅ U ₅ C ₅ g ₅ g ₅ cUGAUgagccgcuuaggccGaa Uguacu B	9503	Amberzyme
141	HCV+	GAGCCAUAGUGGU	4702	22551	a ₅ C ₅ C ₅ a ₅ cu cUGAUgagccgcuuaggccGaa Uggcuc B	9504	Amberzyme
156	HCV+	GCGGAACCGGUGA	4703	22552	U ₅ C ₅ a ₅ C ₅ cg cUGAUgagccgcuuaggccGaa Uuccgc B	9505	Amberzyme
155	HCV+	UGCGGAACCGGUG	4704	22553	C ₅ a ₅ C ₅ C ₅ g ₅ g ₅ cUGAUgagccgcuuaggccGaa Uccgca B	9506	Amberzyme
289	HCV+	GUGGUACUGCCUG	4705	22554	C ₅ a ₅ g ₅ g ₅ ca cUGAUgagccgcuuaggccGaa Uaccac B	9507	Amberzyme
297	HCV+	GCCUGAUAGGGUG	4706	22555	C ₅ a ₅ C ₅ C ₅ cu cUGAUgagccgcuuaggccGaa Ucaggc B	9508	Amberzyme
166	HCV+	GUGAGUACACCGGAA	4707	22556	U ₅ U ₅ C ₅ C ₅ g ₅ g ₅ u cUGAUgagccgcuuaggccGaa Uacucac B	9509	Amberzyme
141	HCV+	AGAGCCAUAGUGGUC	4708	22557	g ₅ a ₅ C ₅ C ₅ acu cUGAUgagccgcuuaggccGaa Uggcucu B	9510	Amberzyme
156	HCV+	UGCAGAACCGGUGAG	4709	22558	C ₅ U ₅ C ₅ a ₅ ccg cUGAUgagccgcuuaggccGaa Uuccgca B	9511	Amberzyme
155	HCV+	CUGCGGAACCGGUGA	4710	22559	U ₅ C ₅ a ₅ C ₅ cg cUGAUgagccgcuuaggccGaa Uccgcag B	9512	Amberzyme
289	HCV+	UGUGGUACUGCCUGA	4711	22560	U ₅ C ₅ a ₅ g ₅ g ₅ ca cUGAUgagccgcuuaggccGaa Uaccaca B	9513	Amberzyme
297	HCV+	UGCCUGAUAGGGUGC	4712	22561	g ₅ C ₅ a ₅ C ₅ ccu cUGAUgagccgcuuaggccGaa Ucaggca B	9514	Amberzyme
168	HCV+	GAGUACACCGGAAU	4713	22562	a ₅ a ₅ U ₅ U ₅ ccg cUGAUgagccgcuuaggccGaa Uguacu B	9515	Amberzyme
166	HCV-	UCCGGUGUACUCA	4714	22563	U ₅ g ₅ a ₅ g ₅ ua gccgaaagg CgagugaGguCu accgga B	9516	Zinzyme
168	HCV-	AUUCGGUGUACU	4715	22564	a ₅ g ₅ U ₅ a ₅ ca gccgaaagg CgagugaGguCu cggaau B	9517	Zinzyme
138	HCV-	ACU AUGGCUUCUCC	4716	22565	g ₅ g ₅ a ₅ g ₅ ag gccgaaagg CgagugaGguCu cauagu B	9518	Zinzyme
156	HCV-	UCACCGGUUCCGC	4717	22566	g ₅ C ₅ g ₅ g ₅ aa gccgaaagg CgagugaGguCu cgguga B	9519	Zinzyme
236	HCV-	GCGGGGGCACGCC	4718	22567	g ₅ g ₅ C ₅ g ₅ u gccgaaagg CgagugaGguCu cccgcg B	9520	Zinzyme

279	HCV-	CACAAGGCCUUUC	4719	22568	g _s a _s a _s -a _s g _s gccgaaagg C gagugaGguCu cuugug B	9521	Zinzyme
151	HCV-	GGUCCGCAGACC	4720	22569	g _s g _s u _s c _s ug gccgaaagg C gagugaGguCu ggaacc B	9522	Zinzyme
292	HCV-	UAUCAGGCAGUAC	4721	22570	g _s u _s a _s c _s ug gccgaaagg C gagugaGguCu cugaua B	9523	Zinzyme
289	HCV-	CAGGCAGUACAC	4722	22571	g _s u _s g _s g _s ua gccgaaagg C gagugaGguCu ugccug B	9524	Zinzyme
166	HCV-	UUCCGGUGUACUC	4723	22572	g _s u _s g _s -a _s g _s ua gccgaaagg C gagugaGguCu accgaa B	9525	Zinzyme
279	HCV-	CCACAAGGCCUUUCG	4724	22573	c _s g _s a _s a _s agg gccgaaagg C gagugaGguCu cuugugg B	9526	Zinzyme
156	HCV-	CUCACCGGUUCCGCA	4725	22574	u _s g _s c _s g _s gaa gccgaaagg C gagugaGguCu cggugag B	9527	Zinzyme
138	HCV-	CACUAUGGCUCUCCC	4726	22575	g _s g _s g _s -a _s g _s ag gccgaaagg C gagugaGguCu cauagug B	9528	Zinzyme
151	HCV-	CGGUUCCGCAGACCA	4727	22576	u _s g _s g _s u _s cug gccgaaagg C gagugaGguCu ggaaccg B	9529	Zinzyme
292	HCV-	CUAUCAGGCAGUACC	4728	22577	g _s g _s u _s a _s cug gccgaaagg C gagugaGguCu cugauag B	9530	Zinzyme
289	HCV-	UCAGGCAGUACCACA	4729	22578	u _s g _s u _s g _s gua gccgaaagg C gagugaGguCu ugccuga B	9531	Zinzyme
168	HCV-	AAUUCCGGUGUACUC	4730	22579	g _s a _s g _s u _s -aca gccgaaagg C gagugaGguCu cggaaau B	9532	Zinzyme
163	HCV-	GGUGUACUCACCG	4731	22580	c _s g _s g _s u _s ga cUGAU G aggccguuaggccGaa Uacacc B	9533	Amberzyme
159	HCV-	UACUCACCGGUUC	4732	22581	g _s a _s c _s c _s cg cUGAU G aggccguuaggccGaa Ugagua B	9534	Amberzyme
140	HCV-	CCACUAUGGCUCU	4733	22582	a _s g _s a _s g _s cc cUGAU G aggccguuaggccGaa Uagugg B	9535	Amberzyme
281	HCV-	ACCACAAAGGCCUU	4734	22583	a _s a _s g _s g _s cc cUGAU G aggccguuaggccGaa Uguugu B	9536	Amberzyme
233	HCV-	GGGGCACGCCCAA	4735	22584	u _s u _s g _s g _s gc cUGAU G aggccguuaggccGaa Ugcccc B	9537	Amberzyme
143	HCV-	AGACCACUAUGGC	4736	22585	g _s c _s a _s a _s ua cUGAU G aggccguuaggccGaa Uggucu B	9538	Amberzyme
146	HCV-	CGCAGACCACUAU	4737	22586	a _s u _s a _s g _s ug cUGAU G aggccguuaggccGaa Ucuugc B	9539	Amberzyme
195	HCV-	CCAAGAAAGGACC	4738	22587	g _s g _s u _s c _s cu cUGAU G aggccguuaggccGaa Ucuugg B	9540	Amberzyme
194	HCV-	CAAGAAAGGACCC	4739	22588	g _s g _s g _s u _s cc cUGAU G aggccguuaggccGaa Uucuug B	9541	Amberzyme
283	HCV-	GUACCACAAGGCC	4740	22589	g _s g _s c _s c _s uu cUGAU G aggccguuaggccGaa Ugguaac B	9542	Amberzyme
286	HCV-	GCAGUACCACAAG	4741	22590	c _s u _s u _s g _s ug cUGAU G aggccguuaggccGaa Uacugc B	9543	Amberzyme
296	HCV-	ACCCUAUCAGGCA	4742	22591	u _s g _s c _s c _s ug cUGAU G aggccguuaggccGaa Uagggg B	9544	Amberzyme
190	HCV-	AAAGGACCCGGUC	4743	22592	g _s a _s c _s c _s g _s cUGAU G aggccguuaggccGaa Uccuuu B	9545	Amberzyme
163	HCV-	CGGUGUACUCACCGG	4744	22593	c _s c _s g _s g _s uga cUGAU G aggccguuaggccGaa Uacaccg B	9546	Amberzyme
140	HCV-	ACCACUAUGGCUCUC	4745	22594	g _s a _s g _s -a _s gcc cUGAU G aggccguuaggccGaa Uaguggu B	9547	Amberzyme
159	HCV-	GUACUCACCGGUUCC	4746	22595	g _s g _s a _s a _s cug cUGAU G aggccguuaggccGaa Ugaguac B	9548	Amberzyme
233	HCV-	GGGGCACGCCCAAA	4747	22596	u _s u _s g _s g _s g _s cc cUGAU G aggccguuaggccGaa Ugcccc B	9549	Amberzyme
143	HCV-	CAGACCACUAUGGCU	4748	22597	a _s g _s c _s -a _s ua cUGAU G aggccguuaggccGaa Uggucug B	9550	Amberzyme
146	HCV-	CCGCAGACCACUAUG	4749	22598	c _s a _s u _s a _s gug cUGAU G aggccguuaggccGaa Ucuugcg B	9551	Amberzyme
195	HCV-	UCCAAGAAAGGACCC	4750	22599	g _s g _s g _s u _s ccu cUGAU G aggccguuaggccGaa Ucuugga B	9552	Amberzyme
283	HCV-	AGUACCACAAGGCCU	4751	22600	a _s g _s g _s c _s cuu cUGAU G aggccguuaggccGaa Ugguaac B	9553	Amberzyme
281	HCV-	UACCACAAGGCCUUU	4752	22601	a _s -a _s g _s g _s gcc cUGAU G aggccguuaggccGaa Uguggua B	9554	Amberzyme
296	HCV-	CACCCUAUCAGGCAG	4753	22602	c _s u _s g _s c _s cug cUGAU G aggccguuaggccGaa Uagggug B	9555	Amberzyme

286	HCV-	GGCAGUACCACAAGG	4754	22603	c ₅ c ₃ u ₅ u ₅ gug cUGAUGgagccguuagccGaa Uacugcc B	9556	Amberzyme
7985	HCV-	UCUCAGU G UCUCUCCA	4765	22719	uggaaga uGAUg gcaUGcacuaugc gCg acugaga B	9557	G-cleaver
4832	HCV-	UGUAUAG CCUCUCC	4755	22720	ggagagg uGAUg gcaUGcacuaugc gCg auauaca B	9558	G-cleaver
4153	HCV-	ACCGUGU G CCUUAGA	4756	22721	ucuaagg uGAUg gcaUGcacuaugc gCg acacggu B	9559	G-cleaver
3200	HCV-	GUGGAGU G AGGUGGU	4757	22722	accaccu uGAUg gcaUGcacuaugc gCg acuccac B	9560	G-cleaver
1682	HCV-	ACGAGU G AACCCUGU	4758	22723	acagguu uGAUg gcaUGcacuaugc gCg aacucgu B	9561	G-cleaver
896	HCV+	CCUGUGU G ACCAUCC	4759	22724	ggauggu uGAUg gcaUGcacuaugc gCg agacagg B	9562	G-cleaver
2504	HCV+	UCCUGUGU G CUUUUCC	4762	22725	ggaaga uGAUg gcaUGcacuaugc gCg aacagga B	9563	G-cleaver
2651	HCV+	UCCUCGU G UUCUUUCU	4763	22726	agaaaga uGAUg gcaUGcacuaugc gCg acgagga B	9564	G-cleaver
4094	HCV+	ACAAAGU G CUCGUCC	4760	22727	ggacgag uGAUg gcaUGcacuaugc gCg acuuugu B	9565	G-cleaver
8970	HCV+	GCCACUU G ACCUACC	4761	22728	gguaggu uGAUg gcaUGcacuaugc gCg aaguggc B	9566	G-cleaver
1200	HCV+	CUUCCUC G UCUCUCA	4789	22747	ugagaga gccgaagg CgagugaGGuCu gaggaag B	9567	Zinzyme
1211	HCV+	CUCAGCU G UUCACCU	4790	22748	agguaga gccgaagg CgagugaGGuCu agcugag B	9568	Zinzyme
2504	HCV+	UCCUGUU G CUUUUCC	4762	22749	ggaaag gccgaagg CgagugaGGuCu aacagga B	9569	Zinzyme
2651	HCV+	UCCUCGU G UUCUUUCU	4763	22750	agaaaga gccgaagg CgagugaGGuCu acgagga B	9570	Zinzyme
8811	HCV+	CACUCA G UCCACUC	4764	22751	gaguaga gccgaagg CgagugaGGuCu ugagagug B	9571	Zinzyme
8594	HCV-	UCGCCGC G UCCUCUU	4793	22752	aagaga gccgaagg CgagugaGGuCu ggcgcga B	9572	Zinzyme
7985	HCV-	UCUCAGU G UCUCUCCA	4765	22753	uggaaga gccgaagg CgagugaGGuCu acugaga B	9573	Zinzyme
6611	HCV-	CCUCCAC G UACUCCU	4796	22754	aggagua gccgaagg CgagugaGGuCu guggagg B	9574	Zinzyme
5633	HCV-	UCCACAU G UGCUUUG	4766	22755	cgaagca gccgaagg CgagugaGGuCu augugga B	9575	Zinzyme
821	HCV-	UCACGCC G UCUUCCA	4767	22756	uggaaga gccgaagg CgagugaGGuCu ggcgcga B	9576	Zinzyme
870	HCV+	CUCUAUC U UCCUCUU	4768	22775	aagagga CUGAUGAgccguuagccGAA lauagag B	9577	Inozyme
1210	HCV+	UCUCAGC U GUUCACC	4769	22776	ggugaac CUGAUGAgccguuagccGAA lcuagaga B	9578	Inozyme
2642	HCV+	UCCUCUC C UUCUCCG	4770	22777	cgaagaa CUGAUGAgccguuagccGAA lagagga B	9579	Inozyme
5726	HCV+	UCACAGC C UCCAUCA	4771	22778	ugauga CUGAUGAgccguuagccGAA lcuuguga B	9580	Inozyme
8142	HCV+	CUCCACC C UUCUCCA	4772	22779	ugaggaa CUGAUGAgccguuagccGAA lguaggag B	9581	Inozyme
7990	HCV-	UGGUGUC U CAGUGUC	4773	22780	gacacug CUGAUGAgccguuagccGAA lacacca B	9582	Inozyme
7813	HCV-	CUUCGCC U UCAUCUC	4774	22781	gagauga CUGAUGAgccguuagccGAA lgcgaag B	9583	Inozyme
7137	HCV-	ACCUCUC U UCAUCC	4775	22782	ggaugag CUGAUGAgccguuagccGAA lagaggu B	9584	Inozyme
6084	HCV-	UUAUCC A CUGCACA	4776	22783	ugugcag CUGAUGAgccguuagccGAA lgaugaa B	9585	Inozyme
2554	HCV-	CAACAGC A UCAUCCA	4777	22784	uggauga CUGAUGAgccguuagccGAA lcuuguug B	9586	Inozyme
1202	HCV+	UCCUCGU C UCUCAGC	4778	22943	guugaga CUGAUGAgccguuagccGAA Acgagga B	9587	Hammerhead
1607	HCV+	GGCACAU U AACAGGA	4779	22944	uccuugu CUGAUGAgccguuagccGAA Augugcc B	9588	Hammerhead
2639	HCV+	GCAUCCU C UCCUUC	4780	22945	ggaagga CUGAUGAgccguuagccGAA Aggaugc B	9589	Hammerhead
6610	HCV+	GAGGAGU A CGUGGAG	4781	22946	cuccacg CUGAUGAgccguuagccGAA Acuccuc B	9590	Hammerhead
9014	HCV+	GGGCAUU U UCACUCC	4782	22947	ggaguga CUGAUGAgccguuagccGAA Auugcgc B	9591	Hammerhead
8605	HCV-	GACUCGU A GGCUCGC	4783	22948	gcagacc CUGAUGAgccguuagccGAA Acgaguc B	9592	Hammerhead
7983	HCV-	UCAGUGU C UUCCAGC	4784	22949	gcuggaa CUGAUGAgccguuagccGAA Acacuga B	9593	Hammerhead
7136	HCV-	CCUCUCU C UCAUCCU	4785	22950	aggauga CUGAUGAgccguuagccGAA Agagagg B	9594	Hammerhead
6609	HCV-	UCCACGU A UCCUCCA	4786	22951	ugagagg CUGAUGAgccguuagccGAA Acgugga B	9595	Hammerhead
6292	HCV-	CGUGCAU A UCCAGUC	4787	22952	gacugga CUGAUGAgccguuagccGAA Augcagc B	9596	Hammerhead
867	HCV+	UUUCUCU A UCUUCCU	4788	22971	aggaaga GGCTAGCTACAACGA agagaaa B	9597	DNazyme
1200	HCV+	CUUCCUC G UCUCUCA	4789	22972	ugagaga GGCTAGCTACAACGA gaggaag B	9598	DNazyme
1211	HCV+	CUCAGCU G UUCACCU	4790	22973	agguaga GGCTAGCTACAACGA agcugag B	9599	DNazyme

5730	HCV+	AGCCUCC A UCACCAG	4791	22974	cugguga GGCTAGCTACAACGA ggaggcu B	9600	DNAzyme
6533	HCV+	UCAACGC A UACACCA	4792	22975	uggugua GGCTAGCTACAACGA gcuuuga B	9601	DNAzyme
8594	HCV-	UCGCCGC G UCCUCUU	4793	22976	aagagga GGCTAGCTACAACGA gcggcga B	9602	DNAzyme
7810	HCV-	CGCCUUC A UCUCUU	4794	22977	aagagga GGCTAGCTACAACGA gaaggcg B	9603	DNAzyme
7133	HCV-	CUCUCUC A UCCUCCU	4795	22978	aggagga GGCTAGCTACAACGA gagagag B	9604	DNAzyme
6611	HCV-	CCUCCAC G UACUCCU	4796	22979	aggagua GGCTAGCTACAACGA guggagg B	9605	DNAzyme
2300	HCV-	CCUCCAA A UCACAAC	4797	22980	guuguga GGCTAGCTACAACGA uuggagg B	9606	DNAzyme
195	HCV+	GGGUCCU U UCUUGGA	4556	23072	c _S c _S a _S a _S ga cUGAuGaggcgWWWagccGaa Aggacc B	9607	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	23076	WWWVWc _S c _S a _S a _S ga cUGAuGaggcgWWWagccGaa Aggacc B	9608	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	23077	WWWVc _S c _S a _S a _S ga cUGAuGaggcgWWWagccGaa Aggacc B	9609	Hammerhead
195	HCV+	GGGUCCU U UCUUGGA	4556	23086	c _S c _S a _S a _S ga cUGAuGaggcgWWWagccGaa Aggacc B	9610	Hammerhead

lower case = 2'-O-methyl

UPPER CASE = RIBO

B = inverted deoxy abasic

U = 2'-deoxy-2'-amino Uridine

C = 2'-deoxy-2'-amino Cytidine

U = 2'-deoxy-2'-amino Uridine

Z = BRdU (5-bromo-2'-deoxy Uridine)

W = acyclic galactose-amine linker

UNDERLINE = deoxy nucleotide

Table VI: Anti HCV amino containing hammerhead ribozyme and control sequences

pos	RPI#	HCV 5'UTR Site	Ribozyme Sequences (5'-3')	Core	Rz Seq ID
62	12257	HCV-62	G _S C _S G _S ugaa cUGAUGaggccguuaggccGaa AcaguagB	Active	9611
79	12258	HCV-79	a _S u _S g _S gcua cUGAUGaggccguuaggccGaa AcgcuuB	Active	9612
81	12249	HCV-81	C _S C _S a _S uggc cUGAUGaggccguuaggccGaa AgacgcuB	Active	9613
104	12259	HCV-104	G _S C _S u _S gcac cUGAUGaggccguuaggccGaa AcacucaB	Active	9614
142	12250	HCV-142	a _S g _S a _S ccac cUGAUGaggccguuaggccGaa AuggcucB	Active	9615
148	12251	HCV-148	u _S u _S C _S cgca cUGAUGaggccguuaggccGaa AccacuaB	Active	9616
165	12260	HCV-165	u _S C _S C _S ggug cUGAUGaggccguuaggccGaa AcucaccB	Active	9617
192	12261	HCV-192	a _S a _S G _S aaag cUGAUGaggccguuaggccGaa AcccgguB	Active	9618
195	12252	HCV-195	u _S C _S C _S aaga cUGAUGaggccguuaggccGaa AggaccCB	Active	9619
196	12262	HCV-196	a _S u _S C _S caag cUGAUGaggccguuaggccGaa AaggaccB	Active	9620
270	12263	HCV-270	C _S u _S u _S ucgc cUGAUGaggccguuaggccGaa AcccaacB	Active	9621
282	12264	HCV-282	G _S u _S a _S ccac cUGAUGaggccguuaggccGaa AggccuuB	Active	9622
306	12265	HCV-306	C _S a _S C _S ucgc cUGAUGaggccguuaggccGaa AgcaccCB	Active	9623
325	12253	HCV-325	u _S C _S u _S acga cUGAUGaggccguuaggccGaa AccuccCB	Active	9624
330	12254	HCV-330	C _S a _S C _S gguc cUGAUGaggccguuaggccGaa AcgagacB	Active	9625
Control Sequences					
79	13274	HCV-79 AC2	C _S u _S u _S aggu cUAGUGaggccguuaggccGau AguucucB	Attenuated	9626
81	13271	HCV-81 AC	u _S C _S u _S gccg cUAGUGaggccguuaggccGau AgugaccB	Attenuated	9627
142	13270	HCV-142 AC	a _S a _S C _S ccug cUAGUGaggccguuaggccGau AgcucguB	Attenuated	9628
192	13272	HCV-192 AC	a _S g _S u _S agaa cUAGUGaggccguuaggccGau AgcugccB	Attenuated	9629
195	13269	HCV-195 AC	G _S a _S u _S ucca cUAGUGaggccguuaggccGau AcgcgacB	Attenuated	9630
282	13273	HCV-282 AC	G _S C _S C _S auuc cUAGUGaggccguuaggccGau AucuggcB	Attenuated	9631
330	13268	HCV-330 AC	C _S C _S a _S ggcu cUAGUGaggccguuaggccGau AaugcgCB	Attenuated	9632
195	15291	HCV-195 BAC3	u _S C _S C _S aaga cUAGUGacgccguuaggcgGaa AggaccCB	Attenuated	9633
195	15292	HCV-195 SAC3	a _S g _S a _S cuac cUAGUGacgccguuaggcgGaa AcccgagB	Attenuated	9634
330	15294	HCV-330 BAC	C _S a _S C _S gguc cUAGUGacgccguuaggcgGaa AcgagacB	Attenuated	9635
330	15295	HCV-330 SAC	G _S C _S u _S ccga cUAGUGacgccguuaggcgGaa AgacacgB	Attenuated	9636

UPPER CASE = RIBO; lower case = 2'-O-methyl; B = inverted deoxyabasic;

s = phosphorothioate linkage

U = 2'-deoxy-2'-amino uridine

Table VII: Anti HCV site 330 antisense nucleic acid and scrambled control sequences

pos	RPI #	Alias	Antisense Nucleic Acid	Seq ID #
330	17501	HCV.5-330 antisense	G _s T _s G _s C _s T _s C _s A _s T _s G _s A _s T _s G _s C _s A _s C _s G _s G _s T _s C _s T	9353
330	17498	HCV.5-330 antisense	G _s T _s G _s C _s T _s C _s A _s T _s G _s G _s T _s G _s C _s A _s C _s G _s G _s T _s C _s T	9637

pos	RPI#	Alias	Control Sequence	Seq ID #
330	17499	HCV.5-330 scrambled	T _s G _s A _s T _s C _s A _s G _s G _s T _s C _s T _s G _s C _s T _s G _s C _s G _s T _s G _s C	9638
330	17502	HCV.5-330 Scrambled	T _s G _s A _s T _s C _s A _s G _s G _s T _s C _s T _s G _s C _s T _s G _s C _s A _s T _s G _s C	9639

UPPER CASE = Deoxy Nucleotide
s = phosphorothioate

Table VIII: In Vitro Cleavage Data, anti-HCV Enzymatic Nucleic Acids

Seq ID #	RPI#	Motif	Site (+/-)	Enzymatic Nucleic Acid Sequence	% Substrate Cleaved in 3 hours	Substrate Sequence	Seq ID #	Substrate RPI#
9587	22943	Hammerhead	1190 (+)	gcugaga CUGAUGAggcccguuagccGAA Acgagga B	89.67	UCCUCGU C UCUCAGC B	9640	22897
9588	22944	Hammerhead	1595 (+)	uccuguu CUGAUGAggcccguuagccGAA Augugcc B	90.33	GGCACAU U AACAGGA B	9641	22898
9589	22945	Hammerhead	2627 (+)	ggaagga CUGAUGAggcccguuagccGAA Aggaugc B	82.54	GCAUCCU C UCCUUC B	9642	22899
9590	22946	Hammerhead	6598 (+)	cuccacg CUGAUGAggcccguuagccGAA Acuccuc B	78.06	GAGGAGU A CGUGGAG B	9643	22900
9591	22947	Hammerhead	9002 (+)	ggaguga CUGAUGAggcccguuagccGAA Aaugcgc B	81.88	GCGCAUU U UCACUCC B	9644	22901
9592	22948	Hammerhead	818 (-)	gcgagcc CUGAUGAggcccguuagccGAA Acgaguc B	88.34	GACUCGU A GGCUCGC B	9645	22902
9593	22949	Hammerhead	1440 (-)	gcuggaa CUGAUGAggcccguuagccGAA Acacuga B	89.16	UCAGUGU C UUCACGC B	9646	22903
9594	22950	Hammerhead	2287 (-)	aggaua CUGAUGAggcccguuagccGAA Agagagg B	83.43	CCUCUCU C UCAUCCU B	9647	22904
9595	22951	Hammerhead	2814 (-)	ugagag CUGAUGAggcccguuagccGAA Acgugga B	83.25	UCCACGU A CUCCUCA B	9648	22905
9596	22952	Hammerhead	3131 (-)	gacugga CUGAUGAggcccguuagccGAA Augcacg B	86.96	CGUGCAU A UCCAGUC B	9649	22906
9597	22971	DNzyme	855 (+)	aggaga GGCTAGCTACAAACGA agagaaa B	92.11	UUUCUCU A UCUUCCU B	9650	22925
9598	22972	DNzyme	1188 (+)	ugagaga GGCTAGCTACAAACGA gaggaag B	86.38	CUUCCUC G UCUCUCA B	9651	22926
9599	22973	DNzyme	1199 (+)	aggugaa GGCTAGCTACAAACGA agcugag B	83.15	CUCAGCU G UUCACCU B	9652	22927
9600	22974	DNzyme	5718 (+)	cugguga GGCTAGCTACAAACGA ggaggcu B	57.82	AGCCUCC A UCACCAG B	9653	22928
9601	22975	DNzyme	6521 (+)	uggugua GGCTAGCTACAAACGA gcuugua B	75.77	UCAACGC A UACACCA B	9654	22929
9602	22976	DNzyme	829 (-)	aaggaga GGCTAGCTACAAACGA gggcgca B	66.06	UCGCCGC G UCCUCUU B	9655	22930
9603	22977	DNzyme	1613 (-)	aaggaga GGCTAGCTACAAACGA gaaggcg B	71.28	CGCCUUC A UCUCUUU B	9656	22931
9604	22978	DNzyme	2290 (-)	aggagga GGCTAGCTACAAACGA gagagag B	61.60	CUCUCUC A UCCUCCU B	9657	22932
9605	22979	DNzyme	2812 (-)	aggagua GGCTAGCTACAAACGA guggagg B	85.53	CCUCCAC G UACUCCU B	9658	22933
9606	22980	DNzyme	7123 (-)	guuguga GGCTAGCTACAAACGA uuggagg B	34.60	CCUCCAA A UCACAAAC B	9659	22934
9557	22719	G-cleaver	1438 (+)	uggaaga uGAUg gcauGcacuaugc gCg acugaga B	69.88	UCUCAGU G UCUUCCA B	9660	22813
9558	22720	G-cleaver	4591 (+)	ggagagg uGAUg gcauGcacuaugc gCg auauaca B	77.74	UGUAUJU G CCUCUCC B	9661	22814
9559	22721	G-cleaver	5270 (+)	ucuaagg uGAUg gcauGcacuaugc gCg acacggu B	47.37	ACCGUGU G CCUJAGA B	9662	22815
9560	22722	G-cleaver	6223 (+)	accaccc uGAUg gcauGcacuaugc gCg acuccac B	75.84	GUGGAGU G AGGUGGU B	9663	22816
9561	22723	G-cleaver	7741 (+)	acagguu uGAUg gcauGcacuaugc gCg aacucgu B	61.58	ACGAGUU G AACCCUGU B	9664	22817
9562	22724	G-cleaver	884 (-)	ggauggu uGAUg gcauGcacuaugc gCg agacagg B	65.16	CCUGUCU G ACCAUCC B	9665	22818
9563	22725	G-cleaver	2492 (-)	ggaaaag uGAUg gcauGcacuaugc gCg aacagga B	94.66	UCCUGUU G CUUUUCC B	9666	22819
9564	22726	G-cleaver	2639 (-)	agaagaa uGAUg gcauGcacuaugc gCg agagaga B	82.14	UCCUCGU G UUCUUCU B	9667	22820
9565	22727	G-cleaver	4082 (-)	ggacgag uGAUg gcauGcacuaugc gCg acuuugu B	67.20	ACAAAGU G CUCGUCC B	9668	22821

9566	22728	G-cleaver	8958 (-)	gguaggu uGAUg gcauGcacuaugc gCg aaguggc B	81.06	GCCACUU G ACCUACC B	9669	22822
9567	22747	Zinzyme	1188 (+)	ugagaga gccgaaaggCgagugaGGuCu gaggaa B	66.11	CUUCCUC G UCUCUCA B	9670	22841
9568	22748	Zinzyme	1199 (+)	aggugaa gccgaaaggCgagugaGGuCu agcugag B	80.28	CUCAGCU G UUCACCU B	9671	22842
9569	22749	Zinzyme	2492 (+)	ggaaaag gccgaaaggCgagugaGGuCu aacagga B	90.80	UCCUGUU G CUUUUCC B	9672	22843
9570	22750	Zinzyme	2639 (+)	agaagaa gccgaaaggCgagugaGGuCu acgagga B	80.64	UCCUCGU G UUCUUCU B	9673	22844
9571	22751	Zinzyme	8799 (+)	gaguuga gccgaaaggCgagugaGGuCu uggagug B	14.85	CACUCCA G UCAACUC B	9674	22845
9572	22752	Zinzyme	829 (-)	aagagga gccgaaaggCgagugaGGuCu gccgcga B	27.83	UCGCCGC G UCCUCUU B	9675	22846
9573	22753	Zinzyme	1438 (-)	uggaaga gccgaaaggCgagugaGGuCu acugaga B	89.39	UCUCAGU G UCUUCCA B	9676	22847
9574	22754	Zinzyme	2812 (-)	aggagua gccgaaaggCgagugaGGuCu guggagg B	50.40	CCUCCAC G UACUCCU B	9677	22848
9575	22755	Zinzyme	3790 (-)	cgaagca gccgaaaggCgagugaGGuCu augugga B	81.10	UCCACAU G UGCUUCG B	9678	22849
9576	22756	Zinzyme	8602 (-)	uggaaga gccgaaaggCgagugaGGuCu gccguga B	73.47	UCACGCC G UCUUCCA B	9679	22850
9577	22775	Inozyme	858 (+)	aagagga CUGAUGAggcccguuaggccGAA laugag B	87.74	CUCUAUC U UCCUCUU B	9680	22869
9578	22776	Inozyme	1198 (+)	ggugaac CUGAUGAggcccguuaggccGAA lcugaga B	84.55	UCUCAGC U GUUCACC B	9681	22870
9579	22777	Inozyme	2630 (+)	cgaagaa CUGAUGAggcccguuaggccGAA lagagga B	90.12	UCCUCUC C UUCCUCG B	9682	22871
9580	22778	Inozyme	5714 (+)	ugaugga CUGAUGAggcccguuaggccGAA lcuguga B	83.77	UCACAGC C UCCAUCA B	9683	22872
9581	22779	Inozyme	8130 (+)	ugaggaa CUGAUGAggcccguuaggccGAA lguggag B	82.22	CUCCACC C UUCCUCA B	9684	22873
9582	22780	Inozyme	1433 (-)	gacacug CUGAUGAggcccguuaggccGAA lacacca B	87.33	UGGUGUC U CAGUGUC B	9685	22874
9583	22781	Inozyme	1610 (-)	gagauga CUGAUGAggcccguuaggccGAA lgcgaag B	70.67	CUUCGCC U UCAUCUC B	9686	22875
9584	22782	Inozyme	2286 (-)	ggaugag CUGAUGAggcccguuaggccGAA lagaggu B	78.83	ACCUCUC U CUCAUCC B	9687	22876
9585	22783	Inozyme	3339 (-)	ugugcag CUGAUGAggcccguuaggccGAA lgaugaa B	86.93	UUCAUCC A CUGCACA B	9688	22877
9586	22784	Inozyme	6869 (-)	uggauga CUGAUGAggcccguuaggccGAA lcuguug B	90.41	CAACAGC A UCAUCCA B	9689	22878

In vitro cleavage in 50 mM Tris-Cl, pH 8.0, 40 mM Mg²⁺ at 37°, using trace substrate, and enzymatic nucleic acid concentration of 500 nM or greater.

UPPER CASE = RIBO

UNDERLINED = DEOXY

lower case = 2'-O-methyl

B = inverted deoxyabasic

C = 2'-amino C

(+/-) = plus strand/minus strand of HCV genome

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms “comprising”, “consisting essentially of” and “consisting of” may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that

the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Other embodiments are within the following claims.